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THE PLACE OF DERMATOLOGY IN A GENERAL HOSPITAL*

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Previous Watson Smith lecturers have all given learned discourses on some branch of dermatology, and as Sydney Thomson in 1958 covered so magnificently the facet of skin disease in which I am specially interested I felt justified in breaking new ground in trying to present to this College the position occupied by dermatology to-day, with particular relation to the other branches of medicine. I also feel justified in doing this because I am sure that it is a subject which would have interested the founder of this lecture. Watson Smith began his medical career in Dundee, but after some years migrated to Bournemouth. where he practised as a general physician with an interest in disease of the skin. I have tried to trace the growth of dermatology as a specialized subject in the hospitals of the United Kingdom, and I wrote to the chief administrative officers of all the teaching hospitals to find when a dermatologist, as such, was first appointed to their hospital.

TABLE I.—*Name and Date of Appointment of First Dermatologists to the Teaching Hospitals of Great Britain*

University College Hospital	Sir William Jenner	1859
Charing Cross Hospital	Tilbury Fox	1860
The Middlesex Hospital	Robert Liveing	1879
St. Mary's Hospital	Sir Malcolm Morris	1882
The Westminster Hospital	T. Colcott Fox	1883
St. Thomas's Hospital	Joseph F. Payne	?1884
Edinburgh Royal Infirmary	William Allen Jameson	1884
Liverpool Royal Infirmary	H. Leslie Roberts	1893
Royal Victoria Infirmary, Newcastle	James Linmont	1893
Royal Infirmary, Sheffield	W. Dale James	1893
King's College Hospital	Arthur Whitfield	1899
St. George's Hospital	Wyndham Cottle	1899
Aberdeen Royal Infirmary	John F. Christie	1901
The London Hospital	James H. Sequeira	1902
Radcliffe Infirmary, Oxford	Ernest Mallam	1905
General Hospital, Birmingham	A. Douglas Heath	1906
Guy's Hospital	Sir Cooper Perry	1907
Royal Infirmary, Dundee	W. E. Foggie	1907
St. Bartholomew's Hospital	H. G. Adamson	1908
Bristol Royal Infirmary	J. A. Nixon	1908
Western Infirmary, Glasgow	J. Wyllie Nicol	1909
Manchester Royal Infirmary	William Dyson	1920
Cardiff Royal Infirmary	James Beatty	1923
Royal Victoria Hospital, Belfast	Ivan H. McCaw	1925
General Infirmary, Leeds	John T. Ingram	1927
Addenbrooke's Hospital, Cambridge	C. H. Whittle	1929

It will be seen from Table I that, by good fortune from the point of view of this lecture, the first dermatologist to be appointed to a teaching hospital in this country was appointed in 1859, just one hundred years ago, at University College Hospital. So far as can be ascertained, Sir William Jenner was in no way connected with Edward Jenner, in spite of the rarity of the surname. Sir William Jenner was also physician to the hospital and was later Physician-in-Ordinary to Queen Victoria and to the Prince of Wales. The list contains many names which have a place of honour in British dermatology. It is intriguing to note the wide difference in the time of the establishment of a dermatological appointment in the different teaching hospitals. Such important hospitals as the Manchester Royal Infirmary, Cardiff Royal Infirmary, the Leeds General Infirmary, and Addenbrooke's, did not have a dermatologist as such until after the first world war.

Willan must have been a remarkable man, but though he died in 1812 at the age of 55 it was another 47 years before a dermatologist was appointed to a teaching hospital. It is, I think, fair to assume that it is probable that all the members of the staff, both physicians and surgeons, treated whatever skin diseases came their way. The archivist of St. Bartholomew's Hospital has sent me a very full account of skin diseases in that hospital. As early as 1554 there are records of payments to Elizabeth Hall for treatment of scald heads, and in 1670 Katherine Ingram was in charge of the cure of scald heads at this same hospital. I gather that the fee for cure of each was twenty shillings. Similarly, at St. Thomas's Hospital there is a record of Edmund Hill being appointed surgeon for scald heads in 1567. I suppose that this is one of the earliest examples of "superspecialization."

To return to more modern times, two men—Erasmus Wilson and Jonathan Hutchinson—had a very great influence on British dermatology in the second half of the last century; neither of them was appointed to his hospital as a dermatologist. Erasmus Wilson is described in the *Annals of the Royal College of Surgeons of England* of 1952 as one of the three most munificent benefactors to that College. He founded a chair of dermatology, but this was later expanded—a delightful word—to embrace a professorship in pathology. This embrace was the kiss of death for the dermatological partner.

It is easy to imagine stormy meetings of the hospital staff in the past whenever the subject of appointing a dermatologist was raised, since such an appointment would inevitably affect to a greater or less extent a part of the private practice of the rest of the staff. I **believe that this is the biggest single factor responsible** for the great difference in the time of the establishment of a dermatological post in the various hospitals.

The first dermatologists had a general training in either medicine or surgery, and a similar trend had been happening on the Continent. Later, in the last century, the branch went through the very necessary phase of minute histological investigation and classification to emerge, at any rate in this country, as an integral branch **of general medicine.**

Place of Dermatology To-day

So much for this brief review of the establishment of dermatology as a specialty. Where do we stand

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to-day in the pattern of the hospital? What is the place of this branch, long known as the "Cinderella of medicine"? I feel that we can and must play an important part in the diagnosis and care of the sick, and during the rest of the space at my disposal I hope to try to illustrate this fact.

Since I went to the United Oxford Hospitals in June, 1957, I have kept a note of all the patients I have had referred to me by other members of the consultant staff and also a record of all the cases presenting primarily with a skin lesion which I have referred to other departments. I have analysed the period from June 1, 1957, to September 30, 1958. The figures do not include the 131 cases I referred to the radiotherapist nor the 48 cases referred to the plastic surgeons, since these were referred mainly because of special therapeutic techniques. I also have only included cases which I have seen myself.

TABLE II

Total number of patients referred by consultants of United Oxford Hospitals to dermatologist from June 1, 1957, to September 30, 1958 .. 315

Referring source:	
E.N.T. department	15 (4·6%)
Eye ,,	17 (5·4%)
Gynaecological ,,	39 (12·4%)
Orthopaedic ,,	34 (10·8%)
Paediatric ,,	24 (7·6%)
Physicians	120 (38·0%)
Psychiatrists	4 (1·3%)
Surgeons	62 (19·7%)

During this period I have seen 315 cases referred from other departments, roughly one every working-day. An analysis of the referring department is shown in Table II and, as one would expect, the largest proportion (38%) were referred by the physicians, but cases came from all departments of the hospital.

These 315 cases fall into three groups: the first group consisted of those in which the eruption was directly associated with the main underlying disease, and comprised 52% of the cases; the second group consisted of 43 cases in which the eruption was caused by treatment of the primary disease; and the third was a group of 108 cases in which the eruption was not in any way associated with the primary disease.

Group 1

I feel that in 49 of the 164 cases in the first group the dermatological diagnosis was of positive help either in confirming or even in establishing the diagnosis. It is obviously impossible to give these cases in detail, but I will briefly mention a few.

Illustrative Cases in Group I

Case 1.—A man aged 56 was referred by one of the physicians for advice on his rash. He had been admitted to hospital with auricular fibrillation and cardiac failure, and in addition to the generalized rash which had been present for many years he had moderate splenomegaly. He was found to be suffering from telangiectasis macularis eruptiva perstans with the splenomegaly sometimes found in this condition. The possibility of mast-cell infiltration of the cardiac muscle giving rise to the infiltration can only, I think, be investigated *post mortem*. At present he is very much alive and well.

Case 2.—A man aged 34 was referred from the ophthalmologist by way of the plastic surgeon for advice on the treatment and prognosis of the pigmentation of the right lower eyelid and lower half of the eye. He was found to have a naevus of Ota.

Case 3.—This case of a farmer aged 26 is interesting; he was referred to me by the eye department. The story was that he had been struck on the left upper eyelid by a cow's tail and a few days afterwards this eyelid became swollen, red, and painful. Within five days a firm nodule appeared on the left upper eyelid. I talked to the students about cowpox and orf—he also kept sheep—but it was only later, when my registrar was taking him over to the laboratory for virus studies, that she got the history from him that his baby had been vaccinated three weeks previously and the cow and the sheep were—as it were—red herrings.

Case 4.—Quite soon afterwards I was asked to see a woman aged 30 in the eye hospital who also had primary vaccinia of the left upper eyelid contracted from her recently vaccinated baby.

Case 5.—A man aged 66 was referred to me by one of the house-surgeons for treatment of the warts on his hands. They were in fact arsenical keratoses. This man had had cirrhosis of the liver for a long time with associated oesophageal varices and he has several times nearly lost his life with haematemeses. Mr. Macbeth, the E.N.T. surgeon, was controlling these varices by means of injections. In going into his story it was found that he had had a good deal of inorganic arsenic for treatment of his psoriasis many years ago. I feel that the cirrhosis is probably connected with the arsenic, and, in addition, he has papillomata of the bladder, possibly from the same cause. During this period I have seen two other cases of arsenical keratoses.

Case 6.—This patient was referred by a physician. He was 72 and had had a bromide-arsenic mixture for several years up to the age of 20 for epileptiform fits. He knew that his hands were abnormally dry in 1917, because he remembered that at that time somebody with whom he shook hands made a remark about the abnormal dryness and roughness of his skin. Incidentally, these cases can often be diagnosed by shaking hands. He had had various epitheliomata treated in his skin from time to time, and had an operation for removal of a carcinoma of the oesophagus in 1947. The long survival period from this operation probably indicates that this was also associated with the ingestion of arsenic. The arsenic content of the skin was investigated by Mr. D. Gibbons, of Harwell. This showed no increase in the arsenic content of the skin, and it is interesting to speculate how arsenic can cause these profound epidermal changes, which often only appear many years after ingestion has stopped. One feels that the arsenic must, in some way, alter the normal process of keratinization, perhaps by entering into an enzyme system.

A third case associated with arsenic was that of a woman of 50 who had received that drug years ago when being treated with bromide for epilepsy.

Case 7.—This patient was referred from the dental department, and I have included her because it does not yet appear to be generally recognized that the commonest cause of angular stomatitis, in this country at any rate, is either ill-fitting dentures or, more commonly, specific sensitization to the material of which the denture is made. All the patients I have seen with this condition have had enormous quantities of vitamin B before they were referred to us (Vickers, 1949).

Case 8.—This patient was referred to me by Dr. Coles, but as she had been referred to him by a surgeon I feel justified in including her in this series. The clinical diagnosis made by a surgeon was a melanoma of the forearm with secondary nodules in the surrounding tissues, but she was in fact suffering from the rare condition, fortunately harmless, described by Church and Sneddon (1954) under the name of familial haemartoma. This name was, I believe, coined by running together the two words hamartoma and haemangioma; however, as one of my learned colleagues who read the classics before he became a pathologist pointed out to me, the defect is in the blood vessels and not in the blood, so that a much better name would be familial angiohamartoma. Dr. Coles has subsequently found other members of the family with the same condition.

Case 9.—In December, 1957, Professor Witts asked me to see a patient of his who was suffering from pernicious anaemia. The anaemia was well controlled, but the

condition which was at that time worrying him greatly was extensive psoriasis. This man had previously suffered from hyperthyroidism, which had been treated by thyroidectomy, and the psoriasis had occurred for the first time in his life some time after the operation. When I was in Sheffield, I had under my care a patient with extensive psoriasis following thyroidectomy in which the parathyroids had been damaged; this patient had a low serum calcium which improved—together with the psoriasis—on calciferol. The present patient also had signs of parathyroid deficiency, he gave a positive Chvostek's sign, and his serum calcium was found to be 5.8 mg./100 ml. He was treated with 50,000 units of calciferol daily, and when seen in July, 1958, his psoriasis had practically disappeared and the serum calcium was improving, being 7.7 mg./100 ml. These cases are of interest as indicating possible triggers for the manifestation of psoriasis in a patient prone to develop this condition.

Case 10.—This case, referred by Dr. Victoria Smallpeice, illustrates, I think, the transplacental passage of the L.E. factor. I first saw the baby in August, 1957, when she was aged 3 months. She is the third child of an American who has suffered from subacute disseminated lupus erythematosus for eight years and who, since coming to this country some years ago, has been under the care of Dr. Stephen Gold. She has had L.E. cells in the peripheral blood from time to time and the condition has been controlled by chloroquine When the child was 4 weeks old a scaling area was noticed in the left temporal region and later the right temporal region was affected. When I saw the baby she had a well-defined erythematous slightly scaling eruption on the central part of the face, spreading into the hair margin in the temporal regions, and small erythematous plaques on the abdominal wall which showed slight atrophy. I thought at first that this was some low-grade infective condition, but in the course of three weeks the diagnosis of discoid lupus erythematosus became much more obvious. Examination of the mother's and the baby's blood at this time showed no L.E. cells, but the mother had a leucopenia of 2,600 per c.mm. Perhaps a little influenced by the mother's natural concern, I gave the child 50 mg. of chloroquine daily, and within five days, either because of or in spite of treatment, the rash rapidly improved and it had almost completely disappeared when the chloroquine was stopped after two weeks' treatment. This baby had been exposed to a good deal of sunshine in the first few weeks of life, and I think that since it has been shown by Bridge and Foley (1954) and by Berlyne *et al.* (1957) that the L.E. factor is present for the first few weeks of life in babies born of a mother suffering from systemic lupus erythematosus, it is reasonable to assume that this baby had the L.E. factor when she was exposed to sunshine and discoid lupus erythematosus developed. The infant is now quite well.

Of the 39 patients referred from gynaecologists, 7 were women who had developed an irritable erythematous eruption in the last few weeks of pregnancy. One of these patients had definite erythema multiforme, but in the others the erythema was of the non-specific toxic type. Russell and Thorne (1957) mention this in their paper on herpes gestationis, and it is, of course, sometimes impossible to separate the rash which is directly associated with the pregnancy from a non-specific erythema due to various drugs administered during this time. In all the patients I saw, the eruption subsided within two weeks of delivery and none of them had any blisters. This type of non-specific erythema is probably relatively common.

Many of these cases I have seen are fascinating, but space prevents the telling of them—the reticuloses with skin changes, the patient with erythema nodosum who had sarcoid nodules on the conjunctiva, the man with von Recklinghausen's disease presenting with the possibility of neoplastic change in one of the large neurofibromata, and so on. I should hate you to imagine that I was never wrong.

Case 11.—A woman aged 42 was referred to me by the E.N.T. department. She had been hoarse all her life and had a curious yellowish-brown slightly nodular infiltration of the skin of the neck, the lower half of the face, and the occipital region. In the occipital region there was marked thinning of the hair. I had never seen anything like this before; I made a tentative diagnosis of an unusual variety of pseudoxanthoma elasticum, and a piece of the affected skin was taken for biopsy. A few days later I was walking across the Radcliffe quadrangle when Dr. Robb-Smith hailed me and, in his delightfully diffident way, asked whether this case, whose sections he had been studying, could possibly be Urbach's lipoid proteinosis. This, of course, was the diagnosis.

Group 2

The next group of 43 comprise those in which the rash was associated with the treatment of the primary disease, and in 26 of these cases the rash was thought to be due to drugs either administered by the doctor or taken by the patient to relieve his symptoms, and 17 were cases of dermatitis due to some local application used in treating the primary disease (Table III).

TABLE III.—*Cases Directly Associated With Treatment*

Due to drugs	..	26	Due to local application	..	17
Aspirin	2		Benzocaine	1	
Barbiturate	2		"Embrocation"	1	
Carbromal	4		Flavine	5	
Hormone	1		Iodine	1	
Penicillin	3		Neomycin	1	
Phenolphthalein	2		Penicillin	1	
Sulphonamide	2		"Skin glue"	1	
Unknown	10		Sticking plaster	1	
			Unknown	5	

Of the drug eruptions, the causes are those now commonly seen in dermatological practice; the largest group, labelled "unknown," comprises patients who had received several rash-producing drugs, and, because of their primary condition or distance from Oxford, it was impossible to trace which of the many causes was in fact responsible for the rash. I have the impression that carbromal eruptions are becoming increasingly common. One of these was of interest in that the patient was referred to me by a gynaecologist. I sent a copy of my letter to him to the patient's practitioner, stating that in my view the rash was due to carbromal. I received a rather indignant letter from the practitioner telling me that the only tablets the patient was taking were a hormonal preparation for menopausal symptoms, and later we found that she had been taking "menopax" tablets, which of course contain carbromal. My colleague, Kenneth Crow, has prepared a list of 15 proprietary preparations containing carbromal, and this number must be steadily increasing.

The rash labelled "hormone" was severe acne occurring in a woman having large doses of methyltestosterone for disseminated carcinomatosis following cancer of the breast. One of the phenolphthalein eruptions was in a young infant. This substance has apparently replaced mercury in some of the so-called teething powders. Of the known local applications flavine still tops the list.

Group 3

In the 108 cases seen in which the dermatosis was not in any way associated with the primary disease, the incidence of the various skin diseases is very similar, as one would expect, to that seen in the out-patient department. 28 of the cases had dermatitis or eczema, 17 had psoriasis, 9 acne, 6 warts, and there was a

sprinkling of such conditions as alopecia areata, pityriasis rosea, lichen planus, etc.

So much, then, for cases referred from other departments.

Cases Seen in First Instance by the Dermatologist in Which Eruption was a Manifestation of Internal Disease

TABLE IV.—*Cases Referred to Other Departments* (33)

E.N.T. department ..	2	Paediatric department ..	2
Eye ,, ...	1	Physicians	17
Gynaecological ,, ...	2	Surgeons	9

Another great group consisted of 33 cases sent to the skin department by practitioners with what was found to be a dermatological manifestation of internal disease. I suppose that it is this type of case which adds spice to our out-patient sessions. Just over half were referred by me to one of the physicians, the choice of the physician being determined by his particular special interest. Table IV shows where these 33 patients were sent. The solitary patient referred to the eye department was a young woman with atopic dermatitis in whom bilateral cataracts were developing.

Case 12.—One of the first patients I referred to the surgeons was very intriguing. He was sent to me because of a so-called wart in the umbilicus which had been present for several months. There was certainly a rather fleshy warty nodule in the umbilicus, but, in addition, there was also a fusiform tense midline swelling in the abdominal cavity arising from the pelvis and extending to the umbilicus, and on pressing this swelling turbid fluid could be squeezed out of the nodule. The diagnosis of persistent urachus was made, and this was confirmed at operation by Mr. Mynors, who removed a mass in which a carcinoma had developed in the base of the urachus, and it is probably because of this that the potential space became filled with fluid.

Case 13.—A man was referred to the wart clinic in May, 1958, with the diagnosis of bilateral plantar warts of the big toes. He was found to have perforating ulcers with symptoms of subacute combined degeneration of the cord; he also had obvious profound anaemia. I referred him to Professor Witts, and in addition to pernicious anaemia he was found to have malignant disease of the stomach, though he had no symptoms referable to his stomach. This was removed by Mr. Elliot-Smith, and the patient is very much alive and doing a full day's work. Unlike the classical story of this type of case, the perforating ulcers which were the cause of his seeking medical advice have also healed.

The next type of case is always very satisfactory.

Case 14.—A man came to the out-patient department with the diagnosis of ? papilloma of the submental region. He had the typical sinus on the skin associated with a dental abscess, and, though the teeth appeared to be healthy, *x*-ray examination showed an abscess at the base of the central incisor from which there was a fine track running from the site of the sinus on the skin.

Case 15.—A woman aged 76 was referred to me because of paronychiae. She gave a history of having had Raynaud's disease for many years. There were numerous telangiectases on the face which were of fairly recent origin. Close questioning revealed that she had suffered a good deal from gastro-intestinal disturbance, and systemic scleroderma was confirmed by the physicians. Incidentally, though the association of telangiectasia with systemic sclerosis is well recognized by dermatologists, this association is not stressed in some of the standard medical textbooks.

Other exotic cases were seen and referred to other departments, but I would like to mention two cases in which I made the wrong clinical diagnosis but was saved by dermatological diagnostic measures.

Case 16.—A man aged 48 was referred to the skin department with erythematous patches on the cheeks which had been present for about two weeks. He had no other symptoms. There was a well-defined, erythematous, slightly indurated plaque on each cheek, and I made a tentative diagnosis of early sarcoidosis. A biopsy of the affected skin was done and *x*-ray film of his chest taken. The biopsy was non-specific, but the radiograph showed a large shadow of the left upper chest. He had no symptoms of chest trouble and was doing heavy work as a furniture remover. He was referred to Professor Allison, who resected the whole mass. This was found to be a carcinoma of the left upper bronchus adherent to many structures, including the recurrent laryngeal nerve, which had to be sacrificed. Over a year later the man was working, and, though hoarse, appeared to be very well.

Case 17.—A man aged 50, working as a long-distance bus driver, felt quite well, but had noticed three small indurated plaques on the chest wall for which his doctor had sent him to the skin department. I made the clinical diagnosis of reticulosis. However, his blood count was normal, but biopsy showed that the skin lesions were deposits of a glandular carcinoma. He had no localizing symptoms or signs and was referred to Professor Witts. *X*-ray examination of the stomach showed a marked leather-bottle picture. This man was seen in July, 1957; he died about six months later.

Conclusions

This, then, is the day-to-day type of clinical work which a dermatologist is doing in association with other members of the staff of a large general hospital.

What conclusions can we draw from this survey? The first is that a dermatologist must have a sound training in clinical medicine and that he must be essentially a general physician with a special interest in disease of the skin. I feel in this respect that it would be a retrograde step to introduce a diploma in dermatology. There is no more place for such a diploma than there is for a diploma in, say, cardiology or neurology.

The second conclusion is that the dermatological department must be closely integrated, both physically and spiritually, with the rest of the hospital. The dermatologist must be readily available on the spot for consultation with the rest of the staff if the sick of the area are to be given the benefit of a comprehensive medical service. In this connexion, I was appalled to learn of two recent appointments in dermatology. In one, a dermatologist working mainly in London was appointed to do two sessions in a hospital about 60 miles away; and in the other, the unfortunate young man does one or two sessions in each of a widely scattered group of hospitals. Please do not imagine that I have anything against the people appointed to these posts, but it is physically impossible to give proper dermatological service under such conditions. The whole of the staffing of the country should be critically reviewed. One feels that the number of consultants in dermatology has largely been determined by the numbers in certain areas before the appointed day. This number was based very largely on the amount of private practice which could support a dermatologist, and this does not necessarily bear any close relationship to the needs of the community.

I wish to draw attention to the views expressed by Jonathan Hutchinson in 1887: "Dermatology is no longer to be regarded . . . as a mere matter of giving arsenic and prescribing ointments and lotions, nor, as some, only a stage more enlightened, think, an arena for endless debate as to the arbitrary application of

pedantic names of older or newer coinage. We have got beyond the old classifications, and we are ceasing to be merely empirical therapeutists. We claim for dermatology a foremost place as a branch of scientific medicine, and without hesitation I assert of it that beyond all others it offers attractions to the student of the laws of disease in general, and to the seeker after the causes which disturb health and local nutrition."

That was true 70 years ago and it is true to-day. I feel that the reason why the ideas of the rightful place of dermatology expressed then so forcibly were not fulfilled was entirely a question of economics. In order to make a living in the days preceding the National Health Service the dermatologist had to see an enormous number of hospital patients in addition to those who provided his bread-and-butter. Before the appointed day there were, with very few exceptions, no full-time consultant dermatologists within 100 miles of London, the private patient living in this area preferring to be seen in "Harley Street." The dermatologists of that time were bogged down by the mass of patients, and I am always amazed that so much was accomplished under those circumstances.

We must make sure that this mistake is not repeated in the National Health Service and that an adequate number of consultant posts are created.

The magnificent conference held in Cambridge on the progress of the basic sciences in relation to dermatology was a striking demonstration of the virgin field waiting to be cultivated. We have the men to do it; we must ensure that their zeal is not stifled by financial stringency.

Dermatology will take its rightful place in medicine only if we, as dermatologists, give practical proof of the value of looking at the skin. I have tried to show how this is working in one general hospital. I know that this is being done in many hospitals in the country, and it must be done in all.

By retaining our training in general medicine and by having time to think, we can fulfil the hopes voiced by Dr. Ingram in his presidential address to the Dermatological Section of the Royal Society of Medicine: "Do not let us resist progress; let us embrace and foster research in all directions, but in these days of increasing specialization which tends to forget the patient and does not always regard medicine as a whole, we must be careful to preserve our heritage and graft progress on to that background."

The general physician with an interest in dermatology who founded this lecture would, I am sure, be pleased by the present trend of dermatology in this country, and so, I know, would the man who taught skin diseases to us both—Rupert Hallam.

In conclusion I would like to quote a recently qualified intelligent student who came to me for advice for becoming a dermatologist. In reply to my question of why he was particularly interested in this branch, he said that dermatology is now the least specialized of all branches of medicine.

The Cinderella child is now claiming the glass slipper, perhaps with the National Health Service as fairy godmother.

I thank all my colleagues on the staff of the United Oxford Hospitals who have been so kind to me since I joined them and who have asked me to see and allowed me to quote their cases; and the administrators of the teaching hospitals who answered my queries so promptly.

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THE BRAIN AND MENTAL RETARDATION*

BY

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Interest in the neural abnormalities associated with and often responsible for mental retardation is gradually increasing, and recent years have also seen a welcome convergence upon this subject by workers in widely separated fields.

The more common encephalopathies of mental retardation have been described from time to time—for example, Crome (1957) and Norman (1958)—while very detailed reviews of the subject by German authors are being published in the still incomplete compendium edited by Scholz (1956). Since neural malformations comprise the bulk of these encephalopathies, the full survey of this particular problem by Ostertag (1956), a contributor to the above compendium, is especially noteworthy, though many of the conditions considered by him are too severe for prolonged or, indeed, any post-natal survival. An outcome of the anatomical studies so far has been a descriptive classification of the anomalies. This is based on normal embryogenesis, many aberrations of development being "timed" in relation to certain stages of brain growth and differentiation.

In regard to aetiology, attention has long been centred on "endogenous" or genetic factors. In animals, such as mice or guinea-pigs, it is possible to produce neural (and somatic) malformations by selective breeding, and some of these—for example, hydrocephalus in mice—may be compared with certain forms of the human disease (Grüneberg, 1947). The resemblance is, however, remote, and at best only suggestive. More direct study of the causes of mental retardation and neural malformations in man reveals the great complexity of the genetic and environmental factors involved (Penrose, 1954).

Realization that maternal rubella and irradiation can act as teratogenic agents has stimulated search for further environmental causes. Experimental work has been fruitful. It is now established that many foetal anomalies may be produced at random or by design when pregnant animals are exposed to different drugs—especially the "antimetabolites"—for example, aminopterin, galactoflavin, acetylpyridine, methylfolic acid—as well as oxygen deprivation, irradiation, and deficiency or excess of certain vitamins in the diet. The literature on this subject is already voluminous and has not yet been comprehensively reviewed, but it may be useful

*Based on a paper read at a Fountain Hospital Evening Meeting on March 20, 1958.

to refer to the following sources: Hicks (1955), Giroud and Lefèbvres (1957), and Millen and Woollam (1957). This work is beginning to stimulate epidemiological investigation into human congenital disease (McDonald, 1958; Record, 1958).

At the same time, and independently, recognition of the social and medical importance of mental retardation has also been growing. Since this is still unmatched by adequate pathological knowledge, it seems useful to present some of the known facts and to restate outstanding problems on the basis of new material.

The Investigation

The material examined comprised 282 brains (mostly with spinal cords) obtained at necropsy on patients at the Fountain Hospital (240 cases), and other hospitals (42 cases). All patients dealt with under the Mental Deficiency Act were included in this series irrespective of their mental level. Only eight of the children not coming under the Act showed marked and lasting mental deterioration or retardation.

The ages of the patients are given in Table I. The mental level was as follows: idiots 146; imbeciles 93; feebleminded, educationally subnormal or normal 9; not assessed 34. The material is thus heavily biased in favour of the younger and more severely handicapped patients.

TABLE I.—*Ages of the* 282 *Patients*

< 1 year	14	3–4 years	34	11–20 years	41
1– years	47	4– ,,	29	Over 20 ,,	19
2– ,,	33	5–10 ,,	60	Not stated	5

Examination was by usual pathological and neurohistological methods. Some of the brains were studied in considerable detail, others only partially. Nevertheless, the examination is regarded as adequate in all cases for purposes of classification in this report. It is continuing, and further study might necessitate minor revision of some of the entries and tabulated results. This possibility was kept in mind in formulating conclusions. Some of the cases have been presented in other communications, and an earlier review of part of the material has also been published (Crome, 1954a).

All cases examined fell into two broad groups. The first (Table II) included instances of clearly defined diseases or syndromes, and each case was entered only once under the appropriate heading. The second group (Table III) included all the brains showing diverse structural abnormalities or none, obtained from patients of no distinct clinical pattern. Most of these brains presented multiple lesions, making it often impossible to classify the specimens under one heading only. The main changes were therefore entered, if necessary, under several appropriate headings. For example, a case showing reduction in weight, gliosis, and cavitation of the brain provided three separate entries.

The obvious limitation of the series is its smallness in relation to the large number of mentally retarded individuals in the community or special hospitals. It does not include, for example, a single certain instance of rubellar embryopathy, though there were 11 such cases at one time or another in this hospital. (Subclinical infection of the mother cannot, of course, be excluded as a cause of some of the encephalopathies in the series.) It includes only one case of phenylketonuria, though this is, with the exception of mongolism, the largest single clinical group at this hospital. The material lacks also examples of irradiation embryopathy, Sturge–Weber disease, and some other rarer syndromes. However, examination of brains is of necessity slow, and, small as it is, the series is among the largest studied in relation to mental deficiency.

Another limitation is that the study is concerned with the frail and young minority rather that the more robust and able majority of mentally handicapped individuals. For this very reason, however, it is full of pathological interest and lends itself most profitably to morphological study.

TABLE II.—*Classified Syndromes.* 91 *Cases* (32.3% *of Total*)

Mongolism	36	Post-encephalitic encephalopathy	3
Hypertensive hydrocephalus	21	Cretinism	2
Tuberous sclerosis	7	Phenylketonuria	1
Gargoylism	4	Laurence–Moon–Biedl syndrome	1
Leucodystrophy	4	Hallervorden–Spatz disease	1
Cerebral lipidosis	3	Hydranencephaly	1
Residual kernicterus due to Rh incompatibility	3	Dermatomyositis	1
Residual kernicterus (not Rh)	1	Acrocephaly-syndactyly	1
		Central neurofibromatosis	1

TABLE III.—*Incidence of Main Abnormalities in* 191 *Unclassified Cases* (67.7% *of Total*)

Micrencephaly (176 brains weighed):		Calcification	15
Under 90% of average	142	Meningeal fibrosis	14
,, 80% ,, ,,	106	Marbling	14
Compensatory hydrocephalus	103	Incomplete cyclopia	6
Gliotic encephalopathy	63	Pachygyria	2
Marked smallness of corpus callosum	42	Ectopic nodules of grey matter	2
Optic abnormality	40	Porencephaly	2
Sundry abnormalities of form	33	Absence of corpus callosum without cyclopia	2
Cerebellar agenesis or atrophy	21	Arhinencephaly without cyclopia	2
No abnormality other than smallness	16	Megalencephaly (over 130% of average)	2
Microgyria	15	Gliosis with giant nerve cells	2
Gross cavitation of brain	15	No abnormality at all	8

Classified Syndromes

Cases in this series were grouped in appropriate syndromes when they appeared to share significantly certain clinical, morphological, and, possibly, aetiological characteristics. What constitutes a syndrome is sometimes obvious but occasionally uncertain and debatable. Mongolism and gargoylism, for example, are clearly distinct entities, while, on the other hand, some morphological changes, such as microcephaly, seem to be merely common signs shared by patients with very varied conditions.

Hydrocephalus

The position of other conditions, such as hydrocephalus, is uncertain. The aetiology of hydrocephalus is manifold, but it is convenient from the viewpoint of clinical management to treat the "hypertensive" type as one group. Such cases (Table IV) present at one time or another signs of raised intracranial pressure, usually with enlargement of the head and evidence of obstruction somewhere in the pathway of the C.S.F. or, more rarely, its over-secretion or under-absorption. In this they differ from the more common "compensatory hydrocephalus," which is considered with the unclassified cases in the next section. It is thought that the head of an infant with ununited sutures may enlarge to some extent and, for a time, without permanent damage to the brain. The cases of hydrocephalus in

TABLE IV.—*Hypertensive Hydrocephalus* (21 *Cases*)

With spina bifida cystica and Arnold-Chiari malformation (1 with retrolental fibroplasia)	8
Post-meningitic (3 after tuberculous meningitis)	7
After haemorrhage	2
With cerebellar agenesis and malformation of toes	1
With occipital meningocele	1
With cerebellar aplasia and spina bifida cystica but no Arnold-Chiari malformation	1
With no significant history and no demonstrable obstruction	1

this series, and probably most of the others with mental retardation, show, however, real secondary cerebral atrophy and other neural damage. This may be extreme, as in hydranencephaly, in which most of the cortex is the thickness of tissue-paper. Whether hydranencephaly is merely an extreme variant of hypertensive hydrocephalus or a separate disease is, however, still uncertain (Crome and Sylvester, 1958).

Hydrocephalus has often been produced in animals experimentally: by selective breeding (Grüneberg, 1947) and by excess or deficiency of vitamin A and B (Millen and Woollam, 1957; Giroud and Lefèbvres, 1957). It is difficult to compare with each other the types of hydrocephalus so produced, since anatomical details are usually omitted in the reports. Many seem to have been of the hypertensive variety, though obstruction in the C.S.F. pathway was not usually demonstrated. It is, of course, still more difficult to relate the experimental results to human conditions, and this problem is referred to again below.

Mongolism

Mongolism, the commonest single disease in low-grade mental deficiency, is still the enigma that it was, in spite of closer study. Its neural morphological changes are characterized by slight reduction in the weight of the brain and smallness of the frontal lobes and cerebellum: the ontogenetically and phylogenetically newer parts of the encephalon. The frequency of associated congenital heart defects—16 out of 36 cases in this series—suggests that the initial causative disturbance operates already at a very early stage of intrauterine life. Both hereditary and environmental factors are probably involved in its causation, as evidenced by the study of mongolism in twins and sibships, and its greater frequency among the children of older mothers.

Tuberous Sclerosis

The clinical and morphological features of tuberous sclerosis are too well known to call for much comment here. The chief neural change consists in the presence of hard glial nodules in many parts of the brain, and the condition is often associated with facial "adenoma sebaceum" and diverse malformations in other organs. A full review of this disease is available in German (Hallervorden and Krücke, 1956). Since the changes in the brain and other organs are so striking, it is perhaps surprising that no analogous condition has yet been reported in animals.

Residual Kernicterus

The most conspicuous lesions—loss of neural parenchyma with glial replacement—in residual kernicterus are found in the globus pallidus and corpus luysii, but the cerebral cortex, particularly the hippocampus, may also be involved. The frequent deafness is possibly caused by lesions in the cochlear nuclei, but this requires confirmation. In this series three cases were due to rhesus-factor incompatibility and one was of unknown origin. It is now generally recognized that while most of these cases of kernicterus are accounted for by blood-group incompatibility and prematurity, some are due to rarer causes—for example, hereditary spherocytosis, inclusion disease of infants, hepatitis, and other infection. The aetiology may also remain undetermined (Boon, 1957). Considerable advance has been made in the understanding of the pathogenesis of the condition (Billing, Cole, and Lathe, 1957). It was established that neural damage occurs when the excessive bile pigment produced by haemolysis (fat-soluble, indirect bilirubin) fails to be conjugated with glucuronic acid in the liver to form glucuronide (non-fat-soluble, directly reacting bilirubin). Hence it is hepatic inadequacy which is decisive in the inadequate disposal of the excessive fat-soluble and, presumably, neurotoxic pigment.

Leucodystrophy

The main change in the leucodystrophies is progressive diffuse degeneration of the white matter in the cerebral hemispheres. The grey matter is also often involved, but to a much smaller extent. Formerly all these cases were grouped together as "Schilder's disease," but it is now believed by some workers (Poser and Bogaert, 1956) that this group contains three separate diseases: early forms of disseminated sclerosis, leucodystrophy proper, and sclerosing leuco-encephalitis (van Bogaert's and Dawson's type of leuco-encephalitis with inclusion bodies). The leucodystrophies are often familial, and were so in two of the four cases in this series.

Cerebral Lipidoses

The specific lesion of the cerebral lipidoses is widespread distension of neurons by adventitious sudanophilic substances. The nerve cells gradually perish, and this is accompanied by marked glial proliferation and, eventually, dense scarring and contraction leading to considerable micrencephaly and ulegyria. Some brains in the recorded instances of neuronal lipidosis were, contrariwise, large, and a number of these showed spongy degeneration of the tissue. This group of diseases includes the variants of amaurotic family idiocy (Tay–Sachs disease) with retinal involvement and often a characteristic cherry-red spot at the macula; Niemann–Pick disease, with notable enlargement of the spleen and lymph nodes; and Gaucher's disease, in which neural change is inconstant. Variants of cerebral lipidosis in older individuals have also been described. The chemical composition of the adventitious intracellular substance is believed to be different in these diseases.

None of the three cases in this series could be classified with precision. One, following rhesus factor incompatibility and neonatal jaundice, showed the typical neuronal change, diffuse retinal atrophy without any macular lesion, and the presence of some adventitious cells in the spleen and lymph nodes without significant macroscopic enlargement of these organs. The second case showed typical neuronal change without involvement of the reticulo-endothelial system or retina. The third was clinically a case of Tay–Sachs disease with progressive mental deterioration and macular lesion; histologically, neuronal distension was absent, nerve cells showing merely a moderate excess of lipochrome pigment. This limited experience suggests that the morphologcial distinction between the different cerebral lipidoses may not always be as clear-cut as is often believed.

Gargoylism

Neuronal lipidosis, very similar to Tay–Sachs disease, has been observed in two unrelated dogs (Hagen, 1953), but it is not known if other members of the litters were affected and, if so, whether recessive inheritance was as aetiologically important as it is in the human condition. Neuronal lipidosis is often but perhaps not invariably present in gargoylism. When this is so,

affected nerve cells cannot be distinguished histologically from those in the other lipidoses. All the four cases in this series showed this change, but one of these was "incomplete," lacking the usual corneal and skeletal involvement of gargoylism.

Unlike the other lipidoses, neuronal changes in gargoylism are often not as widespread, and the brain is not appreciably reduced in weight. A characteristic feature of the brain in gargoylism is perivascular "lacunation," or formation of reticulated cavities around blood-vessels in the white matter. This change is, however, unspecific, occurring also in other conditions.

Other Abnormalities

Of the remaining cases the three with post-encephalitic encephalopathy followed respectively measles, whooping-cough, and, presumably, von Economo's encephalitis. Chronic inflammatory changes were present in all these cases. The case of dermatomyositis presented widespread large areas of focal necrosis in the brain, brain-stem, and cerebellum in varying stages of organization. The case of central neurofibromatosis showed several associated neural changes and was reported fully elsewhere (Crome, 1954b), while the examination of the case of Hallervorden–Spatz disease is not yet complete.

Thus all the cases discussed so far in this section showed definite and, usually, marked neural involvement. The series included, however, also a few instances of syndromes in which such changes are known to be less constant—namely, cretinism, phenylketonuria, Laurence–Moon–Biedl syndrome, and acrocephaly-syndactyly.

No specific or characteristic change has been so far described in the brains of cretins. These are often entirely normal, showing only slight or uncertain "degeneration" of nerve cells. One of the two cases in this series was that of a woman aged 53, whose brain showed bilateral massive calcification of the cerebellar white matter. In the second case the brain showed, pending fuller examination, only uncertain increase in the lipochrome content of nerve cells.

The position in regard to phenylketonuria is somewhat similar. The one case included here showed no certain change after a searching examination. (Three further cases have come to necropsy after the conclusion of the series. All showed some smallness of the brain—71%, 89%, and 90% of the average weight for age—the first was regarded clinically as microcephalic. Only one of these brains has so far been examined histologically, showing no detectable change.) Some of the previous reports on phenylketonuria also mentioned reduction in brain weight as well as pallor or myelin-staining, and, more recently, lack of pigmentation of the substantia nigra and locus caeruleus. Some of these changes have not yet been confirmed in adequately controlled series.

The shape of the brain in acrocephaly-syndactyly is greatly altered, in conformity with the outlines of the "tower"-shaped skull, but no certain histological abnormality of neural tissue has been recorded. The weight of the brain in the present case was within normal limits, and on dissection it presented no abnormality other than the already mentioned peculiarity of shape.

Comment on the Classified Syndromes

It may thus be concluded that the brain is structurally abnormal in most of the classified syndromes. In a few, however, changes are more uncertain, and it is noteworthy that some of these syndromes are characterized by biochemical or endocrine aberration—namely, cretinism, phenylketonuria. It seems reasonable to infer that the mental deficit in such cases may result from a biochemically imperfect functioning of a structurally normal or, at any rate, not strikingly abnormal brain. The reason that the brain is relatively normal may lie in some cases in the ability of the mother's liver to prevent the accumulation of toxic metabolites and thus to prevent the foetus from the consequences of his own metabolic errors. Biochemical disorder also plays a part in certain of the other syndromes accompanied by definite and marked structural change—for example, the lipidoses—and may be suspected to do so in others, like mongolism. In such conditions mental retardation is possibly the result of both sets of factors, structural and chemical. Often, however, and particularly among the unclassified cases to be considered next, structural abnormality is so gross as to obviate the need for any further hypothetical factors in explaining the mental deficit.

Unclassified Cases

Abnormalities in the brains of low-grade patients are, as already mentioned, usually multiple. They often vary from area to area, and, since it is almost impossible to examine the entire central nervous system fully, only the most conspicuous changes could be listed in Table III. In particular, no special study was made of lesions in the brain-stem and spinal cord, and these are not therefore listed separately.

The commonest single abnormality in this large group of cases was reduction in the weight of the brain compared with the average normal weights for the age as quoted by Coppoletta and Wolbach (1933). A breakdown of the weights is given in Table V.

TABLE V.—*Weights of* 176 *Brains, Expressed as Percentage of Average*

%	<40	40–	50–	60–	70–	80–	90–	100–	110–	120–	130+
No.	7	11	18	21	49	36	17	12	2	1	2

Microencephaly and Compensatory Hydrocephalus

Below a certain arbitrarily chosen level the brains may be regarded as micrencephalic. Thus, 106 of the 176 brains weighed less than 80% of the average normal, but allowance must be made for the still uncertain overlap between "normality" and "micrencephaly": hence not every brain weighing less than, say, 80% of the average is necessarily abnormal, and not every brain weighing more than that is normal. However, the weights, as recorded here, mostly underexpress the degree of smallness, since this was usually accompanied by compensatory hydrocephalus, and the remaining fluid in the dilated ventricles was weighed with the brains. In this series all the brains were radiographed after removal and the photographs so obtained provided ready means of assessing the degree of ventricular dilatation, present in 103 cases. This was classified as follows: slight (ventricles dilated but do not exceed a quarter of the total brain area in the skiagram), 33 cases; moderate (not exceeding half of the total brain area), 33 cases; and marked (over half of total brain area), 37 cases. Cases of compensatory hydrocephalus are distinguished from the hypertensive variety, already considered, by absence of head enlargement or other

evidence of past or present rise in intracranial pressure and of anatomical obstruction. They are invariably associated, and commensurate with, agenesis or atrophy of the contiguous solid parts.

Though weights of foetal brains are not usually reported in publications dealing with the experimental production of neural malformations, illustrations and the recorded weights of whole animals leave little doubt about the smallness of the brain in most cases. "Microcephaly" is, indeed, mentioned by name as one of the commonest experimentally produced anomalies, having been observed at one time or another after almost any of the numerous agents employed.

Smallness of the brain in the present series was usually accompanied by some of the other lesions enumerated below. Of these, general or partial reduction in the size of the corpus callosum was particularly constant. Sixteen brains however, showed, no apparent abnormality other than smallness (Table VI). It is

TABLE VI.—*Sixteen Cases With No Structural Abnormality Other than Smallness (Below 90% of Average Brain Weight)*

Imbecile epileptic	83%	Epileptic idiot	86%
Idiot	80%	Feebleminded	85%
,,	73%	Epileptic imbecile	84%
,,	70%	Feebleminded with familial epilepsy	88%
Imbecile	88%	Plagiocephalic imbecile	83%
Feebleminded epileptic	76%	Feebleminded	74%
Feebleminded	77%	,,	76%
Imbecile	81%		
Epileptic idiot	70%		

noteworthy that the smallness was only moderate in this group of cases, the weights ranging between 70 and 80% of the average normal. They did not appear to constitute a special clinical group, presenting varied clinical features and levels of mental disability.

Gliotic Encephalopathy

One of the other frequent findings in micrencephaly, occurring however, also in relatively heavy brains, is gliotic encephalopathy—namely, loss of neural parenchyma and its replacement by glial tissue. Any part of the central nervous system may be so affected, and the stage reached by this process at death varies widely. Usually, in this series, the lesions were "burned out," presenting macroscopic induration with shrinking and discoloration of the affected area, and, microscopically, paucity of nerve cells and their processes with replacement by astrocytes and glial fibres. In the earlier stages there is active breakdown of myelin to neutral fat and phagocytic activity by microglial cells, often accompanied by formation of cavities. The entire brain or any part of it may be affected by gliotic encephalopathy and, accordingly, the condition is referred to as hemiatrophy, lobar sclerosis, ulegyria, or granular atrophy. The basal ganglia, the brain-stem, and the cerebellum may also be involved, and such changes in the last-named account for most of the cases of cerebellar atrophy listed separately in this series. A special variant of gliotic encephalopathy presents with abnormally orientated giant nerve cells (two cases in this series).

Such abnormal cells are also present in tuberous sclerosis and sometimes in pachygyria. Like micrencephaly, gliotic encephalopathy may be the result of many disease processes. It is often said that the human brain does not begin to react to disease or injury in this way until the seventh month of gestation; the earlier reaction being by mere arrest of growth with either subsequent full recovery or far-reaching alteration in the shape of the organ with perhaps local liquefaction and cavity formation. A brain with a malformation acquired in early intrauterine life may, however, sustain further damage later on, and is possibly particularly vulnerable to it. This may explain the not infrequent association of gross "early" malformation with gliotic changes.

Cavitation.—As mentioned already, small cavities are frequent in association with gliosis, and these may contain large numbers of fat-laden phagocytic cells. Cavities may be also present in many other conditions—for example, encephalitis, ischaemic softening, abscesses, leucodystrophy—or in the form of spongy degeneration—"status spongiosus"—attributed by some workers to chronic oedema of the brain. A special form of cavitation—perivascular lacunation—has been mentioned in connexion with gargoylism. While many such forms of cavitation were seen on histological examination in this series, all the 15 cases listed in Table III were of a grosser kind, showing numerous large, often trabeculated, cavities occupying large areas of the brain—"multilocular cystencephaly." Six of these cases had a history of difficult delivery followed by neonatal distress, and the condition may have been due to birth injury. Two of the other cases were probably infective in origin, and the aetiology of the rest was even more obscure.

Calcification.—This is another change associated with destructive lesions and gliosis. It may be apparent, on naked-eye or *x*-ray examination, in such conditions as tuberous sclerosis, Sturge–Weber disease, toxoplasmosis, or inclusion disease of infants. In the unclassified cases under discussion now, four instances of calcification were obvious to the naked eye, the remaining 11 cases coming to light histologically. In these cases calcification was often present in the vicinity of cavities, affecting individual nerve cells, their processes or capillaries. The larger foci of calcified granules were usually situated around the lateral ventricles.

Marbling.—An interesting but not fully understood lesion, sometimes associated with gliotic change and apparently never present without it, is "marbling," also referred to as "état marbré," status marmoratus, or the presence of "plaques fibromyéliniques." This occurs in the cerebral cortex and/or basal ganglia. It presents macroscopically as barely visible whitish streaks perpendicular to the surface of the usually ulegyric cortex, while in the basal ganglia the appearance is of irregularly arranged stouter white bundles, "veins of marble" ramifying upon the background of the gliotic and frequently distorted formation. Microscopically, there is invariable fibrous gliosis and, often, an impression of hypermyelination. Whether there is real excess of myelinated nerve fibres is, however, still questionable. The appearance of hypermyelination may, perhaps, be explained by displacement with condensation of pre-existent myelinated fibres and, at times, the vagaries of myelin staining (Belloni, 1952). Study of our material did not enable us to resolve this question. Whatever the nature of the lesion, it is widely held that the condition is often due to birth injury, and the history of some of the cases in this series is consistent with this view. Nevertheless, birth injury is probably not the only cause of marbling, a recent communication suggesting, for example, that this lesion may originate before birth (Scharenberg, 1957).

It should also be mentioned that slight inflammatory change—namely, leucocytic infiltration, perivascular

cuffing, and the presence of focal aggregations of microglial cells—was not uncommon in this series in circumstances excluding infection as a primary cause of the encephalopathy. In some cases such changes were terminal and in others possibly a reaction to non-septic destructive processes.

While all the changes mentioned so far in this section may be regarded as "reactive" and not different in kind from similar processes originating post-natally, those considered next are clearly of earlier intrauterine onset.

Sundry Abnormalities of Form

Cases grouped under this heading presented one or more of the following changes. (1) Relative smallness of a part of the brain without accompanying gliotic encephalopathy (excluding, however, cerebellar agenesis listed separately). (2) Exaggeration of the downward projection of the medial aspects of the frontal lobes, lending the brain a somewhat simian configuration. (3) Exposure of one or both of the insulae owing to underdevelopment of its operculi. (4) Simplification of the gyral pattern; in particular, underdevelopment of tertiary convolutions. (5) An atypical pattern of gyri—for example, absence or abnormal position of some of the gyri, irregularity in width (poikilogyria), or an excessive number of gyri (polygyria). The last-named is not to be confused with microgyria, which is considered below. (6) An increased ratio of grey to white matter in cross-section of the cerebral hemispheres. (7) Paucity of nerve cells, abnormal cortical lamination, and the presence of abnormally shaped nerve cells.

It was appreciated that some of the above changes, particularly if slight, may also occur as variations of normal brain form and structure. Since it was impossible to control this factor adequately, only the grosser instances were included in the total of 33, which is thus likely to be an underestimate.

Ectopic Nodules, Microgyria, Pachygyria

Ectopic nodules of grey matter, microgyria, and pachygyria may be taken together, since their pathogenesis is probably similar (Crome, 1956). Nerve cells in the embryo proliferate first near the ventricles and then migrate to the periphery, in the cerebrum, to the site of the definitive cortex. Interference with this migration results in failure of the cells to reach their destination and their later development in an abnormal situation. Such abnormal development may lead to the formation of large ectopic nodules near the ventricles, or diffuse neuronal layers within the white matter in cases of microgyria and pachygyria. In both these conditions the ectopic grey matter is separated from the more superficial portion of the cortex by a narrow zone of myelinated nerve fibres. (In addition to these well-defined conditions, it is also common to see fewer nerve cells scattered diffusely and sparsely in the white matter between the ventricles and the cerebral cortex. Some of this is, however, normal in young children and has not been listed as a distinct pathological change in this series.) Recent observations have increased our knowledge of these conditions.

A recurrent association between microgyria and inclusion disease of infants has been reported by Diezel (1954) and confirmed in an unpublished observation by Sabina Strich in this country. Inclusion disease of infants is widely held to be viral in origin. When this is proved, the association will constitute another definite example of viral embryopathy. No case of inclusion disease was found in the present series, but there is nothing to suggest that any malformation is always due to the same cause. Thus, Riggs, McGrath, and Schwarz (1956) were able to produce a condition in rats' embryos very similar to human microgyria and pachygyria by irradiating the pregnant animals five to nine days before birth, and a human case of pachygyria in an infant irradiated during gestation had been previously reported by Uiberrak (1942).

Incomplete Cyclopia Cavitation

Incomplete cyclopia is a convenient but perhaps not scientifically accurate description of the failure of the anterior portions of the two hemispheres to separate normally. (Cases of fuller cyclopia with a single eye and more complete fusion of the hemispheres are known to occur, but no not survive.) The condition was associated in four of the six cases in this series with absence of the olfactory nerves, and in all cases there was partial or complete absence of the corpus callosum, the lateral and third ventricles being represented by a single space. Absence of the corpus callosum (two cases) and absence of the olfactory nerves (two cases) may, however, occur in brains showing full separation of the hemispheres. Malformations somewhat analogous to human incomplete cyclopia have been reported in the offspring of rats kept on a diet deficient in pantothenic acid by Giroud, Delmas, Prost, and Lefèbvres (1957). Several types of absence of the corpus callosum have been described as a spontaneously occurring mutation in mice (King, 1936).

Cavitation of the brain, also referred to as "multilocular cystencephaly," "encephalomalacia," and "encephaloclastic porencephaly," must be differentiated from the rarer instances of porencephaly (two cases in this series) in which unilateral or bilateral funnel-shaped or slit-like clefts traverse much of the cerebral tissue, extending from the meninges up to or into the ventricular cavity. Unlike the "reactive" cavitation, this is a malformation of earlier gestation and is often associated with other gross errors of organ formation, such as microgyria.

One of the two examples listed as "megalencephaly" (brain weight was 130% of average) was associated with dystrophic changes in the white matter (Crome, 1953) and the other (unpublished) with microgyria and glioblastomatosis.

Abnormalities of the Optic System

Finally, it is necessary to mention the frequent association between the encephalopathies discussed above with abnormalities of the optic system. These included cataract (16 cases), retrolental fibroplasia (2 cases), marked microphthalmia (2 cases), coloboma (2 cases), choroidoretinitis (2 cases), and agenesis or atrophy of the more central parts of the optic pathway (40 cases). These figures certainly underexpress the incidence of such lesions, since not all eyes were examined and it is almost impossible to investigate the entire optic pathway fully. Unfortunately little is known of similar auditory abnormalities, since this system is much more difficult to examine anatomically, and no such study was attempted in this series. Deafness is, however, a frequent clinical symptom in mental deficiency, and it is very likely that the auditory system would, when examined, show corresponding changes.

Thus, with the exception of the eight cases showing no structural change whatever, referred to below, and some of the cases listed in Table VI, all the brains of unclassified patients showed obvious and usually gross abnormality, probably sufficient to explain the mental deficit. This is not to say that operation of still unknown biochemical errors can be ruled out in some of the unclassified cases. It is, indeed, safe to predict that new syndromes will in time be recognized among them, and this recognition might well be made by detection of such metabolic errors.

The Brain and Mental Retardation

Possibly the most obvious outcome of this study is the demonstration of the frequency of structural abnormality in the brains of patients with severe mental retardation, and this is in accord with previous experience. Moreover, the changes were usually easily demonstrable by ordinary pathological methods, and it seems likely that future refinements in technique will raise to the surface other, still submerged, anomalies. It is reasonable to infer that the mental deficit in most of these cases is a simple expression of cerebral inadequacy, but other factors, biochemical, metabolic, or endocrine, may well be responsible for both the structural and the functional changes. This is true, for example, of the lipidoses, metabolic disorders leading to progressive mental and morphological changes.

Nevertheless, 8 of the 191 unclassified cases presented no structural change (Table VII), while some of those listed in Table VI showed only slight and possibly

TABLE VII.—*Clinical Features and Percentage of Average Brain Weight in 8 Cases with no Structural Abnormality*

1. Low-grade imbecile, possibly psychotic	104%
2. Unclassified idiot	107%
3. Epileptic	101%
4. Spastic and epileptic idiot	90%
5. Epileptic idiot	92%
6. Educationally subnormal epileptic with cerebral palsy	112%
7. Epileptic feebleminded	102%
8. Imbecile	90%

TABLE VIII.—*Cases Above Imbecile Level*

	Age	Clinical Features	Brain Weight	Pathological Findings
1	5	Epilepsy. Borderline E.S.N. level. Binet I.Q. 54	76% of av. normal	Slight micrencephaly
2	20	Laurence–Moon–Biedl syndrome	79% ,,	Laurence–Moon–Biedl syndrome
3	35	Dull normal to low average. Wechsler I.Q. 79. Matrices 83. Educational deprivation	80% ,,	Slight micrencephaly. Moderate ventricular dilatation
4	53	Feebleminded	82% ,,	Marked ventricular dilatation. Gliotic encephalopathy
5	20	,, epileptic	102% ,,	No structural abnormality
6	3	Educationally subnormal, possibly due to social causes	85% ,,	Slight micrencephaly
7	9	Epileptic, at least E.S.N. level, probably in the dull range	88% ,,	,, ,,
8	4	Epilepsy. Cerebral palsy. Familial. E.S.N. level	112% ,,	No abnormality
9	64	Average intelligence. Wechsler I.Q. 90%. Matrices 105	74% ,,	Slight microcephaly

insignificant reduction in brain weight. Most of these were, rather surprisingly, of low-grade mentality. Since constant structural change has not yet been demonstrated in some of the metabolic disorders associated with mental defect—namely, phenylketonuria, cretinism, galactosaemia, and Laurence–Moon–Biedl syndrome—it is possible that some of the present cases were likewise victims of hitherto unidentified biochemical abnormalities. However, one (Case 1) has been regarded as psychosis due to faulty rearing (Bourne, 1955). This factor may be of major importance in a few other cases of severe mental defect, while it must always be considered in less severely retarded individuals.

It is unfortunate that neither this nor any of the previously published work illumines the numerically major problem of mental retardation: the feebleminded and the educationally subnormal. Only nine such cases could be studied in the present series (Table VIII), and it is impossible, of course, to generalize on this basis. It seems plausible, however, to assume, pending confirmation, that some of the higher-grade mentally retarded individuals would show similar but milder neural changes to the low-grade cases, and that in others they would be entirely undetectable by present methods. The retardation in the latter may then be explained by the cumulative effect of adverse but not individually decisive pathogenetic factors, such as indifferent hereditary endowment, educational deprivation, domestic difficulty, minor disease, and so on. Future work will no doubt clarify this issue.

Aetiology

Scrutiny of the case records in this series revealed many possibly aetiologically significant entries, such as maternal illness before or during pregnancy, antepartem haemorrhage, trauma to mother or child, occasional family history of similar disease, blood-group incompatibility, and so on. The presumed cause could seldom be confirmed by the pathological findings, and it is still impossible to express numerically the relative or absolute incidence of the known causes of mental defect. A valid assessment of the data would require a special study with appropriate controls: this has not been done. The present views on the aetiology of mental defect have been considered by us (Crome and Kirman, 1957).

One of the tasks is to apply the results of the experimental studies and knowledge of the few known causes of congenital neural disease in man to the still unsolved problem of the majority of cases of mental retardation. In some instances the cause may be identical in both experimental and human conditions. We know, for example, of irradiation microcephaly in Japan after the atomic bombardments, and in other countries after the therapeutic application of *x* rays during pregnancy. It seems unlikely, however, that such large doses of irradiation are received with any frequency and could thus account for many cases of mental retardation. But it is possible that in certain circumstances some human embryos are vulnerable to smaller amounts of irradiation. Similarly, though many forms of neural malformation analogous with those occurring in man have been produced experimentally, it does not follow that the same causes—that is, gross vitamin excess or deficiency, anoxia, drugs, selective breeding—operate frequently in an identical manner in man.

Gross dietary vitamin deficiency is probably rare in the more highly developed countries, but conditioned vitamin deficiency is possible in such states as hyperemesis gravidarum, toxaemia, and infection. Vitamins may not be properly utilized or converted into active forms. Hoët (1956, quoted by Giroud and Lefèbvres, 1957) found, for example, carotenaemia in diabetic and pre-diabetic pregnant women and suggested that this is due to failure of full conversion to vitamin A resulting in conditioned vitamin deficiency. Endocrine factors are also known to play a part. Thus Millen and

Woollam (1957) were able to enhance the teratogenic effect of excess of vitamin A by the administration of cortisone and to diminish it by giving insulin. The supply of oxygen and nutrients to the foetus may be impeded or arrested by ante-partum haemorrhage.

Whatever the cause, it need not necessarily produce clinical signs in the mother. It is known, for instance, that the incidence of stillbirths and of congenital abnormality may be raised in an epidemic of German measles in the children of mothers who themselves remain free from overt disease (Lundström, 1952). Again, as in the case of irradiation, some embryos may be rendered vulnerable to a relatively slight deficiency of food or vitamin or oxygen lack through restriction of their adaptive capacity by an unfavourable combination of hereditary and other environmental factors. All these possibilities will no doubt be tested by future work, and steps in this direction are already being taken.

The results of a prospective study by McDonald (1958) and by Record (1958) presented at a discussion at the Royal Society of Medicine suggested, for example, that there may be a significant correlation between maternal tuberculosis and maternal anaemia, and the incidence of stillbirths and major congenital defects. These valuable studies are fraught, however, with many special difficulties and cannot replace the time-honoured careful clinical and pathological case studies. Moreover, it is clear from reported experimental work that genetic factors are by no means unimportant. Different strains of animals often react differently to the same teratogenic agent. It was shown, for example, by Andersen (1949) that the incidence of diaphragmatic hernia produced in the foetus by deficiency of vitamin A in the maternal diet varied from 0.9 to 18.9% in two different strains of rats. The shift in emphasis towards environmental factors in the causation of congenital disease does not obviate the need for further genetic studies, though these will have to be conducted with less exclusiveness than formerly. Clinical experience also suggests that inheritance is decisive in such syndromes as the lipidoses, gargoylism, phenylketonuria, and tuberous sclerosis, and that it may contribute significantly to the causation of many other conditions, including mongolism.

Summary

The morphological findings in 282 brains obtained at necropsy from mental defectives and other mentally retarded individuals, mostly of low grade, fell into two groups: 91 (32.3%) were classified as recognized syndromes with characteristic clinical and pathological disease patterns; and 191 (67.7%) could not be so classified. The neuromorphological features of both groups are briefly described. Most cases showed gross and obvious neural abnormalities, but there were certain noteworthy exceptions. In the group of the classified syndromes a few, such as phenylketonuria and cretinism, are known to be associated with only inconstant and doubtful neural lesions, even though many of the phenylketonuric brains are small. Of the 191 unclassified cases only 8 showed no morphological change, while 16 others presented only some micrencephaly, the weights of the brains ranging from 70 to 88% of the average normal for age. The study thus confirms the widely held view that severe mental retardation is usually associated with encephalopathy. However, in a minority of cases biochemical metabolic errors appear to play a major part, impairing, sometimes severely, the work of structurally not very abnormal brains.

The anatomical basis of the milder grades of mental retardation remains largely unknown.

Advances have been made in the aetiology and pathogenesis of certain conditions associated with mental retardation, particularly by experimental teratologists employing such methods as irradiation, drugs, and excess or restriction of vitamins in the diet of pregnant animals. This knowledge is yet to be extended to human conditions.

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"Pasteur's remark that 'in the field of observation, chance favours only the prepared mind' is so well known that it is almost a scientific cliché. . . . The preparation of a mind is worth some consideration particularly since this topic is frequently neglected in favour of the more striking (if inexplicable) whims of chance. . . . How, then, does one achieve the prepared mind? The more one observes the results of the varied educational experiments that form each department's courses, and the more one studies the lives and achievements of great biologists, the more two features become clear. So far as training is concerned, the essential feature is enthusiasm, whatever the stimulus, and its canalization into some form of biological activity. The second feature is the cultivation of diversity; diversity of reading, of observation, of experiment, of intellectual experience." ("Becoming a Biologist": Professor J. H. Burnett, *The Biological Journal*, Spring, 1960.)

ROLE OF EATON AGENT IN DISEASE OF LOWER RESPIRATORY TRACT

EVIDENCE FOR INFECTION IN ADULTS

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The aetiology of primary atypical pneumonia has been the subject of considerable debate for the past 20 years. Much of this controversy has centred in the agent isolated by Eaton, Meiklejohn, and van Herick in 1944. This agent could be maintained by serial amniotic passages in chick embryos, and its presence was demonstrated by induction of pneumonic lesions in cotton-rats and hamsters inoculated intranasally with suspensions of the chick-embryo tissues. Eaton and his associates also demonstrated that approximately 50% of the sputum or throat-washing specimens from patients with primary atypical pneumonia produced similar lung lesions in hamsters or cotton-rats inoculated intranasally. The specimens which produced the highest rate of pneumonic lesions in animals were those collected during the first few days of illness from patients who developed cold agglutinins. Neutralization tests in animals with paired sera from a limited number of patients suggested that neutralizing antibody increases were found most often in patients who also showed significant rises in cold agglutinins and in agglutinins for *Streptococcus MG*.

In 1957 Liu developed his unique indirect fluorescent antibody technique for the agent isolated by Eaton *et al.* in 1944. Liu studied the 1944 isolate, as well as eight additional strains which he isolated from cases of primary atypical pneumonia in the Boston area, and another strain isolated from the lung of a patient who died in 1943. The nine strains isolated by Liu from cold-agglutinin-positive patients were shown to be antigenically similar to each other and to the 1944 isolate of Eaton *et al.* Later, Liu *et al.* (1959), using the indirect fluorescent antibody test, studied three additional groups of 89 patients with non-bacterial pneumonia and found 67–90% showed rises to the Eaton agent. The development of fluorescent stainable antibody for the Eaton agent paralleled neutralizing antibody for this agent as measured in cotton-rats. This finding provided additional evidence that the individuals who developed fluorescent stainable antibody for the Eaton agent were indeed infected with this agent or an antigenically related agent.

The present investigation, also employing the indirect fluorescent antibody technique, was undertaken to re-examine the role of the Eaton agent in primary atypical pneumonia. Patients who developed cold agglutinins and/or *Streptococcus MG* agglutinins during their convalescence from pneumonia were selected to represent the experience of various years from 1947 to 1959 in various geographical localities. An association of a positive serological response for the Eaton agent in such a diversified group of patients would further strengthen the suggested role of this agent in atypical pneumonia. Individuals with atypical pneumonia unassociated with cold agglutinins or *Streptococcus MG* agglutinins were also studied in order to estimate the potential importance of the Eaton agent in such illness. Evidence that infection with the Eaton agent had occurred concurrent with illness was sought by attempts to recover this agent from the sputum or throat washings of selected patients who developed a positive serological response in the fluorescent antibody test. Such evidence is of some importance, since it has been suggested that the development of fluorescent stainable antibody during convalescence may represent a non-specific response (Dingle and Jordan, 1959).

MATERIALS AND METHODS

Strains of Eaton Agent.—The Mac strain of the Eaton isolated from human lung in 1944 in California by Eaton *et al.* (1945) was kindly furnished by Dr. Eaton. The F. H. strain isolated from sputum (Liu, 1957) was received through the courtesy of Dr. Liu. Two additional new strains of the Eaton agent recently isolated at the National Institutes of Health from pneumonia patients were also included in the study.

Preparation of Pools of Eaton Agent. Inoculation and Harvest of Chick Embryos

All strains of the Eaton agent used were cultivated in 13-day-old white leghorn or Rhode Island Red chick embryos. Using the transillumination technique for amniotic inoculation described by Enders and Habel (1956), 0.1–0.2 ml. of a 10% suspension of infected chick-embryo lung diluted 1:2–1:5 in trypticase soy broth with 0.5% bovine albumin (T.S.B.) was inoculated into each egg. The lung suspensions were maintained in a crushed-ice bath during the time interval required for inoculation. Incubation was at 35° C. for five to six days and the embryos were harvested without previous chilling. For the preparation of a pool of the Eaton agent only the lungs and the lower portion of the trachea were collected from each embryo and ground in 2 ml. of T.S.B. per embryo. The suspension was immediately ampouled in 0.5–2-ml. amounts in glass phials, sealed, and stored in a dry ice-chest (−70° C.) as a stock pool of the agent.

Each passage was checked for bacterial sterility by inoculating thioglycollate broth tubes and blood-agar plates, and 6 to 10 embryos were sectioned and tested for the presence of the agent by the indirect fluorescent antibody test described in a subsequent section. In addition, a passage of the newly prepared stock virus was made into 10 to 12 13-day-old chick embryos to determine the capacity of the pool to produce

subsequent infection of chick embryos. The stock pool was further tested by its ability to induce pulmonary consolidation and pneumonia in intranasally inoculated cotton-rats (*Sigmodon hispidus*) and DBA/2JN mice. Only 20 to 25% of these chick-embryo lung pools of the Eaton agent were satisfactory, and there was a wide variation in the numbers of positive embryos found in any individual pool.

Preparation of Fluorescein-Labelled Anti-Human Globulin

Anti-human globulin sera were prepared by immunizing rabbits with human gamma-globulin (poliomyelitis-immune globulin (Lederle)). The first immunization consisted of a mixture of equal volumes of Freund's complete adjuvant (Difco) and gamma-globulin given in 10 0.1-ml. amounts intradermally. A three-weeks "rest" period was followed by a second immunization consisting of an equal mixture of gamma-globulin and Freund's incomplete adjuvant given in 10 0.1-ml. intradermal doses. This was followed by monthly 1-ml. intradermal injections of gamma-globulin without adjuvant. In some cases a satisfactory anti-gamma-globulin titre was obtained after two months. Other animals required a more lengthy immunization series.

These sera were labelled with fluorescein isothiocyanate by the method described by Marshall *et al.* (1958). Specifically, 5 ml. of serum was mixed with 25.1 ml. of phosphate-buffered saline, *p*H 7, chilled in a crushed-ice bath, and adjusted to *p*H 9 with 3.4 ml. of M/2 carbonate buffer; 16.8 mg. of fluorescein isothiocyanate was added and conjugation was allowed to proceed with constant agitation on a magnetic stirrer at 0–4° C. for 18 to 24 hours. The conjugate was then dialysed against phosphate-buffered saline, *p*H 7, for three to four days to remove free fluorescein isothiocyanate. The fluorescein-labelled serum was absorbed twice with monkey-kidney powder and twice with chicken-liver powder prior to use for fluorescent staining to eliminate non-specific staining properties. The absorbed conjugates were kept at 4° C. for five to seven days or at −20° C. for five to six weeks without a change in their staining properties. The tissue powders were prepared by acetone extraction using standard methods (Coons and Kaplan, 1950).

Indirect Fluorescent Antibody Test for Eaton Agent

The indirect fluorescent antibody test developed by Watson (Weller and Coons, 1954), with its practical application as a serological diagnostic test for primary atypical pneumonia, has been described by Liu (1957) and Liu *et al.* (1959) and was performed in this laboratory according to their methods. In brief, frozen sections of chick-embryo lungs were cut in a cryostat, mounted on glass microscope slides, fixed in acetone for 10 minutes, and allowed to dry. Only those chick-embryo lungs that showed intense fluorescent staining which was specific for the Eaton agent in several bronchioles or air sacs in both the right and the left lung lobes were used. Serial sections were cut and stored at −20° C. One embryo produced 200 to 900 sections (4–6 μ thick). The sections were satisfactory for use in the test for three to four months, though they were usually used in two to three days.

A 1/10 dilution of the convalescent serum of the paired sera under study was used for a preliminary screening test. The 1/10 serum dilutions and all subsequent dilutions were made in guinea-pig complement diluted 1/10 in veronal-buffered saline, *p*H 7. The section was covered with the diluted serum and allowed to react at 37° C. for 30 minutes. The serum was rinsed off and the slide immersed in phosphate-buffered saline, *p*H 7. The slide was then wiped dry except in the area of the chick-embryo lung section, which was then covered with the fluorescein-labelled anti-human conjugate and plated at 37° C. for 30 minutes. The final step consisted in washing the slide for 10 minutes in buffered saline and mounting the section under a coverslip with buffered glycerol, *p*H 7. The slides were then examined for intensity of specific fluorescence in the bronchial epithelial areas at a magnification of 125, using a microscope with an ultra-violet-light source.

The intensity was graded at 1+ to 4+. Sections with no fluorescence in the bronchial epithelial areas were recorded as negative (<10) and no further testing of these sera was performed. The slides were read without knowledge of the serum-donor's clinical diagnosis. A positive control serum was titred in each test and any deviation in the serum titre invalidated the test. A convalescent serum specimen which produced any degree of fluorescence in the screening test was then titred simultaneously with an acute-phase specimen from the same patient. Twofold serum dilutions were used in all tests. The highest serum dilution giving a 1+ staining was taken as the endpoint of the antibody titration. A fourfold increase in antibody titre from the acute to the convalescent specimen was regarded as significant.

Cold Agglutinins and Streptococcus MG Agglutinins

The techniques for the cold agglutination and *Streptococcus MG* tests were those described by Feller (1948).

Complement Fixation

Allantoic fluid, amniotic fluid, and tissue-culture fluid antigens for members of the myxovirus group were prepared as described by Cook *et al.* (1959). The method of preparation of the yolk-sac antigen for Q fever was that of Smadel (1956), for psittacosis that of Meyer and Eddie (1956), and for L.G.V. that of Rake (1956). The preparation of adenovirus antigen has been described by Rowe *et al.* (1955), *Coxsackie B* by Beeman *et al.* (1952) and respiratory syncytial virus (Long strain) by Chanock *et al.* (1957). The Bengsten modification of the complement-fixation test, using 2 full units of complement, 4 units of antigen, and overnight fixation at 4° C., was employed for most tests. The technique of this test has been described in detail by Cook *et al.* (1959). In occasional tests, using Q fever or psittacosis antigens, water-bath fixation at 37° C. for one hour was employed.

Haemagglutination Inhibition

Haemagglutination inhibition tests for the prevalent strains of influenza were used for screening the cold-agglutinin-negative serums. The technique employed was that of Hilleman and Werner (1953).

Animals

The National Institutes of Health line of DBA/2JN mice was used and the cotton-rats were purchased from the University of Michigan. The volume of the intranasal inoculum for the mice varied from 0.05 to 0.1 ml.,

while the inoculum for the rats was 0.5 ml. A group of control animals were inoculated with formalized saline with each group of test animals to check for the presence of latent respiratory agents.

Isolation Attempts

Attempts to isolate Eaton agent were made with two sputum specimens from cases of clinically diagnosed primary atypical pneumonia from 1956 and 1958. The specimens had been stored without antibiotics at −70° C. Eight throat washings from patients with clinically diagnosed viral pneumonia in 1959 who had significant fluorescent antibody rises to the Eaton agent were also examined for the presence of the agent.

The sputums and throat washings were ground in T.S.B. with 2,000 units of penicillin/ml. and inoculated amniotically into six 13-day-old chick embryos, intranasally into four DBA/2JN mice and two cotton-rats, and into tissue cultures of chick-embryo mince, chick-embryo lung, hamster kidney, monkey kidney, chicken kidney, kitten lung, human kidney, and HEP–2 cells. The lungs and trachea of the chick embryos were harvested six days after inoculation and carried through two additional amniotic passages in chick embryos. These embryos were then tested for the presence of the Eaton agent by the indirect fluorescent antibody test, using a 1/20 dilution of a known positive serum which gave definite staining at a 1/320 dilution. The mice and rats were sacrificed 12 to 13 days after inoculation and the lungs were immediately scored for the presence of pneumonia and/or consolidation. The tissue cultures were maintained for 10 to 20 days, and observed for cytopathogenic effect, for haemadsorption by the technique of Vogel and Shelokov (1957), and, when feasible, for fluorescence, using the indirect technique.

RESULTS

Cold-agglutinin-positive or Streptococcus-MG-positive Viral Pneumonia in Adults

A retrospective study was undertaken to correlate the occurrence of cold agglutinins and/or *Streptococcus MG* antibody rises and antibody rises to the Eaton agent in patients with a clinical diagnosis of primary atypical pneumonia. In this survey sera from pneumonia patients in many different geographical areas, both in the United States and in Europe, were tested for evidence of infection with the Eaton agent. Many of the sera were obtained from the Walter Reed Army Institute of Research serum files. The sera from 1947 were kindly supplied by Drs. Floyd Denny and John Dingle. Tables I and II give the results of these tests. Twenty-two patients had antibody rises to the Eaton agent, two had antibody but failed to show a fourfold rise in the fluorescent antibody test, while two were negative for the Eaton agent. These sera were drawn in nine separate years, and antibody rises were demonstrable in every year except 1948, where only one serum pair was available. Eleven of the atypical pneumonia patients showed a rise from <10 to 320+. Six patients showed lower levels of antibody development, while five who possessed antibody in the acute-phase serum had fourfold or greater fluorescent antibody rises. The acute serum specimen of one of the patients who possessed antibody but who did not develop a fourfold rise in antibody was obtained on the 10th day of disease.

Table II shows the correlation of cold agglutinins, *Streptococcus MG* agglutinins, and the Eaton agent antibody rises in clinically diagnosed primary atypical pneumonia in adults. Approximately 85% of the individuals with rises of cold agglutinins and/or *Streptococcus MG* agglutinins developed a rise of

TABLE I.—*Development of Antibody to Eaton Agent in Cold-agglutinin and/or Str.-MG-Agglutinin-positive Atypical Pneumonia in Different Localities and in Different Years*

Date	Location	Age and Sex	Day Disease	Reciprocal of Antibody Titre: Cold Aggl.	Str. MG	Eaton Staining Antibody
1947 Oct.	Cleveland, Ohio	32 M	6	<4	<10	160
			13	256	20	2,560
Nov.	,, ,,	23 F	7	4	<10	<10
			13	256	<10	320
Nov.	,, ,,	45 F	6	<4	<10	<10
			13	512	<10	640
Nov.	,, ,,	27 M	7	<4	<10	<10
			14	1,024	80	640
Dec.	,, ,,	41 F	8	<4	<20	<10
			15	512	<20	640
1948 Dec.	New Jersey	17 M	14	<2	—	<10
			23	32	—	<10
1953 July	Washington (State)	— M	3	<2	16	<10
			21	128	32	80
Nov.	District of Columbia	43 M	3	<2	<8	<10
			63	<2	16	80
1954 May	,, ,,	30 F	4	<2	<8	<10
			23	<2	32	—
			33	—	—	40
Nov.	,, ,,	24 M	6	<2	<8	<10
			23	8	16	—
			41	<2	8	320
1955 July	,, ,,	36 M	4	<2	<8	<10
			24	64	64	—
			47	—	—	160
Sept.	,, ,,	22 M	10	<2	<8	<10
			25	4	64	320
Oct.	New York	23 M	5	32	16	<10
			12	32	64	320
Oct.	Texas	29 M	4	<2	<8	40
			17	64	<8	160
Mar.	Newfoundland	24 M	3	<2	<8	<10
			13	<2	<8	160
			30	4	8	—
1956 Jan.	District of Columbia	23 M	2	<2	<8	<10
			30	<2	32	320
Aug.	Italy	26 M	9	<2	<8	<10
			24	64	256	640
Oct.	District of Columbia	— F	9	<2	<8	<10
			23	64	128	320
1957 Nov.	Oklahoma	22 M	10	<2	<8	80
			16	256	16	—
			40	4	16	160
Dec.	,,	22 M	6	<2	<8	10
			11	<2	<8	80
			25	32	16	—
1958 Jan.	District of Columbia	24 F	7	<2	<8	10
			14	8	64	320
Jan.	Kentucky	23 M	5	<2	<8	<10
			30	8	8	20
July	New York	31 M	9	<2	<8	<10
			36	<2	32	<10
Aug.	Virginia	33 M	6	<2	<8	40
			33	256	<8	80
1959 Jan.	South Carolina	18 M	3	<2	<8	<10
			16	8	8	320+
Feb.	,, ,,	17 M	4	<2	<8	40
			16	64	8	320+

TABLE II.—*Correlation of Rises in Cold-agglutinin, Str. MG, and the Eaton Agent Antibody in Primary Atypical Pneumonia*

Presence of Indicated Antibody		No.	No. with Eaton Antibody
Cold Agglutinins	Str.-MG-Antibodies		
+	+	14	13
−	+	5	4
+	−	7	5

fluorescent stainable antibody for the Eaton agent. A single outbreak or epidemic in which several agents are widely disseminated can often lead to a spurious association of one of the agents with the illness in question. Broader experience, however, with numerous outbreaks or epidemics will often establish the identity of the agent responsible for this illness. Therefore it is important to note that the high level of association of cold agglutinins and/or *Streptococcus MG* antibodies with fluorescent antibody rises to the Eaton agent was maintained over a 12-year period and was observed for patients studied in many different geographical locations, thus minimizing the possibility of such dual infections. These findings confirm and extend the observations reported by Liu *et al.* (1959). When the sera in Table I were tested in complement-fixation tests for antibody rises to influenza A, B, or C, mumps, para-influenza 1 (HA-2), para-influenza 2 (CA), para-influenza 3 (HA-1), adenovirus, L.G.V., and Q fever no serological evidence of infection with these agents was found.

Aetiologically Undiagnosed Pneumonia in the Paediatric Age-group

Previous studies utilizing the cold-agglutinin technique indicated that an appreciable proportion of children developed such antibodies during convalescence from primary atypical pneumonia (Garrow, 1958). It was of interest to determine if the Eaton agent appeared to play a part in viral pneumonia in the paediatric age-group. One hundred and ten children with infection of the lower respiratory tract were studied as part of a continuing collaborative study with the Virus Laboratory of Children's Hospital, Washington, D.C., designed to determine the role of viral agents in childhood respiratory disease. Adenoviruses or myxoviruses were not recovered by standard isolation procedures, and these children failed to develop complement-fixation antibodies for influenza A, B, or C, para-influenza 2 (CA), para-influenza 1 (HA-2), para-influenza 3 (HA-1), respiratory syncytial virus, or adenovirus antigens.

Eighteen (16%) showed at least a fourfold rise to the Eaton agent by the indirect fluorescent antibody test. Eight of these serum pairs which showed high-level rises to the Eaton agent were also tested in complement-fixation tests with L.G.V. and Q fever antigens with negative results. Only one (2.4%) of 42 children whose respiratory illness was associated with para-influenza 1 (HA-2), para-influenza 2 (CA), para-influenza 3 (HA-1), Asian influenza A, or adenovirus, by virus isolation or serology, showed an antibody rise to the Eaton agent. In a group of 64 children with no respiratory illness no fourfold rises to the Eaton agent were noted. The study extended for 16 months, from October, 1957, to January, 1959. The second paper of this series, Chanock *et al.* (1960), will present the detailed serological results, epidemiological data, and clinical information on these children.

Cold-agglutinin- and Streptococcus-MG-negative Viral Pneumonia in Adults

Liu *et al.* (1959), employing cross-adsorption techniques, failed to demonstrate a relationship between fluorescent stainable antibody for the Eaton agent and cold agglutinins or *Streptococcus MG* agglutinins. Furthermore, the occurrence of fluorescent antibody rises to the Eaton agent in pneumonia patients who were negative or failed to show fourfold antibody rises in cold agglutinins or *Streptococcus MG* antibodies has been noted (Liu *et al.*, 1959; Johnson *et al.*, 1960). It was of interest, therefore, to determine how frequently antibody rises to the Eaton agent developed in a series of 69 cold agglutinin- and *Streptococcus - MG* - negative adult patients with pneumonia. Sera from these patients were submitted to the Walter Reed Army Institute for Medical Research over a period of eight years, from 1952 to 1959. Haemagglutination inhibition or complement-fixation tests were negative for Q fever, psittacosis, adenovirus, and the prevalent strains of influenza A and B. Eighteen (26%) developed fourfold or greater rises to the Eaton agent. An additional four individuals showed antibody patterns of <1:10 to 1:10. The patterns of antibody responses in this series are shown in Table III. It will be seen that the level of antibody developed is not unlike that observed in the cold agglutinin- and *Streptococcus-MG*-positive group. It is apparent from the results of this study that antibody rises to the Eaton agent are not uncommon among patients with pneumonia who fail to develop cold agglutinins or *Streptococcus MG* agglutinins.

TABLE III.—*Pattern of Fluorescent Antibody Rise for the Eaton Agent in Cold-agglutinin Negative, Str.-MG-Negative Pneumonia*

No. with Indicated Pattern	Pattern of Fluorescent Antibody Development Acute Serum Titre ——→ Convalescent Serum Titre
4	<10 ——→ 10
2	<10 ——→ 40–80
12	<10 ——→ 320+
3	10 ——→ 40–80
1	40 ——→ 320+
Total 22	

Isolation of Strains of Eaton Agent

Material for isolation attempts was available from one patient who developed a rise in cold agglutinins and from nine patients who did not develop cold agglutinins or *Streptococcus MG* agglutinins. Both new strains of the Eaton agent were isolated from sputum specimens by three amniotic passages in 13-day-old chick embryos. No isolates were obtained from the eight throat-washings examined. The presence of the agent was detected by the use of the indirect fluorescent antibody test using a known positive serum as an indicator of infection. One of the strains (R.J.) from a cold-agglutinin-negative viral pneumonia was also isolated in DBA/2JN mice. Pulmonary consolidation was noted in three-quarters of the animals inoculated. Identification of the mouse isolate was accomplished by passage of the mouse lungs into chick embryos which contained specific areas of fluorescence when tested by the indirect fluorescent antibody technique. The strain from the cold-agglutinin-positive case (L.P.) was not recovered from mice. It was not possible to recover an agent from the lungs of cotton-rats inoculated with the two positive sputum specimens. No evidence of consolidation or pneumonia was seen in these animals, and passages of the lungs into chick embryos failed to result in the recovery of the R.J. strain, the L.P. strain, or any additional strains.

Differences in the ability of strains to propagate in mice and cotton-rats may represent important biological properties or they may be an expression of the number of infectious particles present in the isolation specimens. After three or more passages in chick embryos both strains were capable of producing pneumonia in cotton-rats and mice.

Heretofore all strains of the Eaton agent have been shown to be antigenically indistinguishable (Liu *et al.*, 1959). It was important to determine if the newly isolated strains were also antigenically similar to the strains isolated by Eaton and Liu. Table IV presents the results of reciprocal fluorescent antibody tests in which serial sections of chick-embryo lungs infected with the F.H. strain, the L.P. strain, or the R.J. strain were used to titrate acute and convalescent serum specimens

TABLE IV.—*Antigenic Relationship of Three Strains of the Eaton Agent by Indirect Fluorescent Antibody Technique*

Post-infection Human Serum*	Reciprocal of Fluorescent Antibody Titre with Indicated Strain of the Eaton Agent†		
	F.H.	L.P.	R.J.
Wm.‡	320	320	320
L.P.	640	640	640
R.J.	1,280	640	1,280

* Acute-phase serum gave negative (<1 : 10) results when tested with all three strains of the Eaton agent.

† Individual strains of the Eaton agent were inoculated into 13-day chick embryos and harvested on day 19. Two to three areas of 4+ fluorescence were visible in the bronchial epithelium when tested with a 1 : 40 dilution of Wm. serum in guinea-pig complement.

‡ Human serum used to standardize test throughout entire study period.

from patients L.P. and R.J. and the serum used to control the staining reactions with the F.H. strain. The new strains appear to be antigenically similar to each other and to the older F.H. strain. Since the 12 strains of the Eaton agent isolated from 1943 to 1958 were similar by the fluorescent antibody technique, it would appear that a major antigenic variation has not occurred during this time interval.

Attempts to establish the F.H. or the Mac strain in tissue culture have failed to date in every instance. Tissue cultures of chick-embryo mince, chick-embryo lung, chick kidney, hamster kidney, monkey kidney, human kidney, kitten lung, and HEP-2 cells were employed with many combinations of media *p*H, incubation periods, and serial passage. It was hoped that newly isolated strains which have not been passed extensively in eggs or animals might propagate in tissue culture. Unfortunately this was not the case. No evidence of the Eaton agent could be demonstrated in any of the above tissue-culture systems inoculated with the sputum specimens which yielded positive results in embryonated eggs (R.J. and L.P. strains). Evidence of a specific Eaton agent effect was sought by observation of the tissue cultures for cytopathic effects, haemadsorption, and the indirect fluorescent antibody technique.

Specificity of the Fluorescent Antibody Test for Eaton Agent

Further evidence for the specificity of the fluorescent antibody test for the Eaton agent in human respiratory disease was sought when sera from adults infected with para-influenza 1 (HA-2) (Reichelderfer *et al.*, 1958), para-influenza 3 (HA-1) (Kapikian *et al.*, unpublished data), Asian influenza A (Jap-305-57) (Bell *et al.*, 1957), or adenovirus (Ward *et al.*, 1955 ; Bell *et al.*, 1956) from human volunteer studies were examined for antibody rises to the Eaton agent. All of these individuals developed complement-fixation antibody titres of 1 : 64 or greater to the virus inoculated, and at least a fourfold increase in specific antibody titre. Table V summarizes the results of the fluorescent antibody tests. Of the 13 individuals studied, 38% had antibody for the Eaton agent but no rises were observed.

TABLE V.—*Lack of Fluorescent Antibody Rise to Eaton Agent in Adults Infected with Para-influenza 3 (HA-1), Para-influenza 1 (HA-2), Asian Influenza A, or Adenovirus*

Virus Infection	No. Tested	No. with Antibody Rise	No. with Antibody but No Rise
Para-influenza 3 (HA-1) ..	4	0	2
,, 1 (HA-2) ..	5	0	2
Asian influenza A	2	0	1
Adenovirus	2	0	0
Total ..	13	0	5 (38%)

Fourteen serum pairs from cases of Q fever and six serum pairs from psittacosis patients (three of these serum pairs were received from Dr. K. F. Meyer) also failed to show antibody rises to the Eaton agent in the indirect fluorescent antibody test.

Prevalence of Fluorescent Antibodies to Eaton Agent in a General Population Group

Studies currently in progress designed to determine the role of the Eaton agent in respiratory disease in military recruits stimulated a serological survey to determine the frequency of Eaton antibody in various age-groups. This information is of importance in establishing a general baseline for comparative studies involving other populations and other time intervals. Serum specimens obtained in 1957 from a group of persons in the upper middle-income bracket living in Montgomery County, Maryland, were tested at a 1/10 dilution for the presence of Eaton antibody. Table VI presents the results of this

TABLE VI.—*Frequency of Fluorescent Antibody to Eaton Agent in Persons in Upper Middle Income Brackets in Montgomery County, Maryland,* 1957

Age in Years	No. of Persons Tested	No. with Eaton Agent Antibody	Percentage Positive
0– 2	20	0	0
3–10	20	3	15
11–19	20	3	15
20–24	5	2	40
25–29	15	6	40
30–39	20	4	20
40–49	20	4	20
50–59	17	3	18
60–69	15	0	0

152 35

survey. By 3 years of age 15% of the individuals tested were positive for Eaton antibody and the percentage of individuals with antibody remained at least at this level until the age of 59. The greatest prevalence of antibody to the Eaton agent occurred in the 20–29-year-old age-group, but the differences in different age-groups are not significant. Liu *et al.* (1959) have shown that antibody levels for the Eaton agent decrease rapidly after three to four months, but no information is available on the time interval required for conversion to a negative antibody status. Antibody to the Eaton agent has been shown to be present, however, for a year or longer after the illness (Liu *et al.*, 1959 ; Johnson *et al.*, 1960). For this reason it is not possible to interpret the data in terms of age-specific infection rates. The data are consistent with Eaton's (1950) observation that primary atypical pneumonia may affect any age-group but that there is some evidence for a diminished susceptibility of those over 30 years of age.

Seasonal Incidence of Infection with Eaton Agent

Some respiratory agents (influenza A, B) have a seasonal incidence, show periodic antigenic shifts, and occur in epidemic spurts, while others—para-influenza 1

(HA-2) and para-influenza 3 (HA-1)—have been shown to occur in every month of the year and have not appeared to exhibit major antigenic variations (Chanock, unpublished data). The Eaton agent appears to be similar in these respects to the latter group. In Table VII, where the antibody rises to the Eaton agent have been grouped by months, it can be seen that they could be demonstrated in every month of the year with the exception of April, when only one specimen was tested.

TABLE VII.—*Seasonal Incidence of Fluorescent Antibody Rises to the Eaton Agent*

Status		Month												Total All Mths.
		J	F	M	A	M	J	J	A	S	O	N	D	
Cold-agglutinin and or Str.-MG-positive	No. tested	4	1	1	0	1	0	3	2	1	4	6	3	26
	No. positive	4	1	1	0	1	0	3	2	1	4	6	3	26
Cold-agglutinin and Str.-MG-negative	No. tested	10	14	4	1	2	7	5	4	6	5	8	3	69
	No. positive	5	5	0	0	1	3	1	1	3	1	1	1	22
Total ..	No. tested	14	15	5	1	3	7	8	6	7	9	14	6	95
	No. positive	9	6	1	0	2	3	4	3	4	5	7	4	48

DISCUSSION

A serological study of adult patients with atypical pneumonia who developed cold agglutinins and/or *Streptococcus MG* agglutinins indicated that the development of antibody to the Eaton agent was a fairly consistent finding. Of 26 such patients, 22 developed antibody for the Eaton agent demonstrable by the indirect fluorescent antibody technique. Such positive serological responses to the Eaton agent were observed for patients whose illness occurred during various years from 1947 to 1959 and in various geographical areas. These findings minimize the possibility of a spurious association of the syndrome of cold agglutinin- and *Streptococcus-MG*-positive atypical pneumonia with an antibody rise for the Eaton agent. Positive serological responses to the Eaton agent, however, were not limited to adult pneumonia patients who developed cold agglutinins and/or *Streptococcus MG* agglutinins. Twenty-six per cent of the pneumonia patients studied from 1952 to 1959 who failed to develop cold agglutinins or *Streptococcus MG* agglutinins and whose illness could not be attributed to influenza A or B, adenovirus, psittacosis, or Q fever also developed a serological response for the Eaton agent.

Additional evidence associating infection leading to the development of Eaton antibody and respiratory illness was obtained in a controlled study of aetiologically undiagnosed lower respiratory disease in infants and children. Antibody rises to the Eaton agent were observed almost exclusively in the patients whose illness was aetiologically undiagnosed, rarely among patients whose respiratory disease was associated with myxovirus or adenovirus infection, and not at all among infants or children without respiratory illness. The detailed findings and a discussion of these results will be presented in the second paper of this series.

Present evidence indicates that the antibody to the Eaton agent as measured by the fluorescent antibody technique is a specific one. Thus, adults infected with para-influenza 3, influenza A or adenovirus who developed high levels of homologous antibody failed to develop antibody to the Eaton agent. Similarly, persons infected with psittacosis virus or *Coxiella burnetii* failed to develop antibody for the Eaton agent, confirming the findings of Eaton (1950) and Liu (1957). In addition, adult pneumonia patients who developed antibody for the Eaton agent failed to develop antibody for influenza, para-influenza, adenovirus, psittacosis, or *Coxiella burnetii.*

Agents immunologically indistinguishable from the Eaton agent were recovered in embryonated eggs from 2 of 10 patients with pneumonia who developed antibody to this agent. This observation confirms the findings of Eaton and of Liu, and suggests that infection with this agent occurred concurrently with pneumonia. This interpretation is also at variance with the suggestion that the development of antibody to the Eaton agent represents a non-specific response (Dingle and Jordan, 1959). The total number of isolations of the Eaton agent is sufficiently limited, however, so that acceptance of this interpretation must await more extensive experience with specimens obtained from carefully controlled studies involving persons with and without respiratory illness.

Liu demonstrated that the nine strains he recovered from patients with primary atypical pneumonia were antigenically indistinguishable from each other and from the prototype strain of Eaton. The two isolates recovered in this investigation were indistinguishable from one of Liu's strains. The failure to detect antigenic variation among strains of the Eaton agent recovered from 1943 to 1958 is consistent with the sporadic occurrence of cold-agglutinin positive pneumonia in the civilian population and the persistent rather than epidemic occurrence of primary atypical pneumonia positives in a military population now under surveillance (Chanock *et al.*, unpublished data).

SUMMARY

Considerable serological evidence for the association of the Eaton agent and viral pneumonia with or without cold agglutinins or *Streptococcus MG* antibody rises was obtained by use of the indirect fluorescent antibody test. In two instances serological rises to the agent were substantiated by isolation of a strain of the Eaton agent from the sputum of the patient. Antigenic variation and non-specific reactions could not be demonstrated. Prevalence of fluorescent antibody to the Eaton agent in a general population group suggests that it is a widespread and common infection which may occur in all age-groups. Infection with the agent may occur in any month of the year.

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TRANSIENT AMINO-ACIDURIA IN SEVERE POTASSIUM DEPLETION

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Severe potassium depletion can produce gross clinical disturbance with weakness, paralysis, and mental confusion. The condition can arise in primary renal disease (Schwartz, 1955) and also from extrarenal causes (Black, 1957). Confusion arises because potassium loss from extrarenal causes can result in renal dysfunction with albuminuria and impaired ability to concentrate or excrete an alkaline urine (Relman and Schwartz, 1956).

Urinary amino-acid loss has been described in the nephrotic syndrome (Blainey, 1954; Tegelaers, and Tiddens, 1955; Stanbury and Macaulay, 1957), and in the tubular nephropathies (Milne, Stanbury, and Thomson, 1952; Bickel, Smallwood, Smellie, and Hickmans, 1953).

The case reported here showed, in association with potassium depletion, gross amino-aciduria which disappeared on correction of the potassium deficit.

Case Report

A 72-year-old woman was admitted to hospital as an emergency with the sudden onset of confusion and weakness 12 hours previously. A history was obtained from her relatives of cough, sputum, and breathlessness for 12 years, with intermittent ankle oedema for four weeks. Albuminuria had been noted in hospital seven years previously (acute bronchitis), but not one year previously (pneumonia). The patient had been taking digitalis since 1951 and had had 5 g. of chlorothiazide over the five days prior to admission. Diet was adequate and included two cooked meals with first-class protein and green vegetables daily. She had had no diarrhoea nor did she use purgatives.

On examination she was confused and drowsy. The mouth temperature was normal, the respiratory rate was 18 a minute, and she had a regular pulse rate of 66 a minute, with occasional extrasystoles. The arterial blood-pressure was 170/90 mm. Hg, and her heart was slightly enlarged, with, on auscultation, an apical grade II systolic murmur which had been noted in 1951. A few scattered rales were heard at the lung bases and there was slight pitting oedema of the ankles. Apart from her abnormal mental state, clinical examination of the central nervous system showed nothing abnormal, and no abnormality was found in any other system.

Extensive routine haematological and biochemical investigation showed no abnormalities except in the levels of serum electrolytes, which were Na, 105 mEq/l.; K, 3.8 mEq/l.; and Cl, 73 mEq/l. There was no respiratory acidosis present as judged by arterial CO_2 content and *p*H, and liver-function tests and oral glucose tolerance were normal.

Chest radiography suggested that the lungs were emphysematous and that the left ventricle was enlarged. The first electrocardiogram showed prolongation of the Q–T interval and prominent U waves. The urine showed no albumin or sugar and no formed elements at any time, but the specific gravity was fixed between 1009 and 1011 for at least the first 17 days after admission. The main abnormalities are recorded in Table I.

TABLE I.—*Findings During Potassium Depletion and After its Repletion*

Features	During Potassium Depletion	After Treatment[1]	Comments
Serum Na (mEq/l.) ..	105	130	
,, K ,, ..	3·8	4·2	
,, Cl ,, ..	73	100	
E.C.G.: Q-T c.sec. ..	0·47	0·41	Progressive shortening of Q-T c. and disappearance of U waves. Lead V^5 used throughout
U waves ..	Prominent	Absent	
R.B.C. potassium mEq/l. R.B.C.[2]	78 (Day 1)	99 (Day 35)	R.B.C. chloride and sodium both fell with treatment
Muscle intracellular potassium[3] mEq/l. intracellular water	155·6 (Day 1)	175·8 (Day 37)	
Muscle intracellular potassium[4] mEq/kg. dry weight	324·0 (Day 1)	433·0 (Day 37)	
Muscle intracellular acidosis	Present	Absent	High intracellular chloride taken to indicate acidosis[5]
Urinary excretion of potassium	<Intake	≏ Intake (Day 35)	
Amino-aciduria ..	Significant (Day 11)	Normal (Days 32, 33, and 85)	See Table II
Maximum specific gravity of urine	1,010	1,016	
Albuminuria	Nil	Nil	
Creatinine clearance, ml./min.	75 (Day 10)	53	Over a four-hour period
Clinical condition ..	Confused, weak, paranoid	Mentally clear and co-operative; no weakness	

[1] Day 43 unless otherwise stated.
[2] Mean normal value = 98·2 mEq/l. R.B.C. (Flear, Hughes, and Quinton, 1958).
[3] Mean normal value for intracellular potassium = 154·4 mEq/l. intracellular water (Crampton, Flear, and Matthews, 1960).
[4] Mean normal value = 329·7 mEq/kg. dry weight (Crampton *et al.*, 1960).
[5] Inulin space taken as measure of extracellular space (Crampton and Flear, 1958).

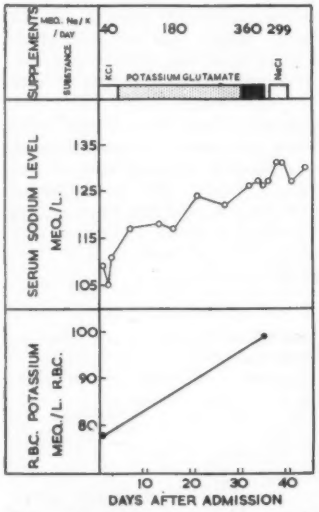
Diagnosis, Treatment, and Course

Definite diagnosis of potassium depletion is difficult, and in practice a provisional diagnosis is usually made from the simultaneous occurrence of a number of non-specific findings (Flear, 1958), or from a history suggesting potassium loss or deficient intake.

Though a careful appraisal of the clinical history and past treatment in this case failed to suggest any obvious reasons for potassium depletion,* the electrocardiographic pattern was suggestive of potassium deficiency and the serum electrolyte pattern was compatible with this diagnosis. The mental state also pointed to some severe metabolic disturbance, and a diuretic known to cause potassium loss had been given.

The serum potassium level was within normal limits, but serum potassium levels are unreliable in the detection of *cellular* potassium depletion (Moore, Edelman, Olney, James, Brooks, and Wilson, 1954; Burrows and Ross, 1956; Flear *et al.*, 1957).

Confirmatory evidence was sought by muscle biopsy, and though this did not show a lowering of intracellular potassium content or concentration (see Table I), it also does not exclude potassium deficiency (Flear, 1958). The muscle biopsy suggested the presence of intracellular acidosis, another finding compatible with potassium depletion. The R.B.C. potassium at 78 mEq/l./cells was definitely low, a finding we have not observed except in potassium depletion.



Changes in serum sodium and red-cell potassium while receiving added potassium. The patient was grossly confused and psychotic when treatment was begun and for several days thereafter. Serum potassium levels were within the normal range except for a rise to 6.7 mEq/l. during the five days of very heavy potassium supplements.

On the basis of these abnormalities a therapeutic trial of potassium therapy was decided upon and treatment with potassium supplements was followed within four days by rapid clinical improvement with disappearance of mental confusion, increase in strength and well-being, loss of oedema, and the development of a voracious appetite. These changes were accompanied by progressive return of the E.C.G. and serum biochemistry towards normal (see Fig.). Serum potassium levels showed a significant upward trend from 3.8 mEq/l. (day 1) to 5.7 mEq/l. on the 27th day of treatment.

One of us (K. W. D.) had suggested a renal tubular defect as the cause of the potassium loss and that amino-aciduria should be looked for. Dr. J. D. Blainey kindly carried out this investigation, and gross amino-aciduria was found (Table II).

A strong point against the diagnosis of a primary renal tubular dystrophy as the cause of the potassium loss was the continuous retention of potassium as shown by daily fluid and electrolyte balance charts.† In addition there were no associated abnormalities such as glycosuria, proteinuria, cysteinuria, or corneal cysteine deposits, one or more of which usually accompany primary tubular defects.

*The amount of chlorothiazide (5 g.) which had been given was thought to be far too small for the diuretic to be entirely responsible for the potassium depletion.

†Full details of the 24-hour urinary output of electrolytes and fluid balance can be supplied to any interested reader.

TABLE II.—*Pattern of Amino-aciduria Found on Paper Chromatography*

Amino-acids	Day 11	Days 32 and 33	Day 85
Cysteic acid	Trace	Trace	Trace
Glycine	++	+	"
Serine	++	–	"
Taurine	+	+	–
Glutamic acid	++	–	–
Proline	++	–	Trace
Histidine	Trace	–	"
Valine	"	–	–
Lysine	++	–	–
Arginine	++	–	–
Glutamine	+++	–	–
Threonine	++	–	–
Alanine	++	Trace	Trace
Tyrosine	++	–	–
Leucine	Trace	–	–
β-Hydroxy-*n*-butyric	+–	–	–

Total 24-hour urinary output. By comparison with taurine standards: Trace = 5 μg.; + = 5 μg.; ++ = 10 μg.; +++ = 20 μg.

By the 27th day of treatment, during which time 4,300 mEq of potassium had been given as supplements to a normal ward diet, the serum sodium had stabilized around 125 mEq/l. (see Fig.). The urinary findings suggested that potassium supplements were still being retained while sodium intake and excretion approximately balanced. To establish whether this low serum sodium level was the normal for this patient, and further to decide whether potassium deficiency was still present, potassium supplements were increased to 360 mEq/day for five days (days 30–35) then sodium supplements of 299 mEq/ day were substituted for the potassium for four days while fluid intake was kept constant; finally all supplements were stopped.

On added potassium the urinary potassium remained considerably lower than intake until the fifth day. During sodium supplements on a fixed fluid intake, marked thirst was experienced and the serum sodium level rose to 130 mEq/l., while most of the added sodium was excreted in the urine. Without supplements the serum sodium level and urinary sodium excretion reverted to pre-trial levels while loss of potassium in urine fell to low levels.

Further urinary chromatograms at this stage showed that the abnormal amino-aciduria had disappeared.

These findings suggested: (1) the persistence of some potassium depletion, at least until the fifth day of the large potassium supplements (day 35); (2) the absence of significant sodium depletion; (3) that the patient's normal serum sodium level was low (see Fig.) (and compare the values at out-patient follow-up on day 85; Na = 127 mEq/l., and one year later Na = 130 mEq/l.); and (4) that the potassium loss was not due to primary renal disease.

A second muscle biopsy and further studies on whole blood and red cells (Table I) confirmed the retention of potassium which had taken place.

Discussion

The total amount of potassium given as supplements over 35 days was 6,640 mEq. This was in addition to the intake of potassium in a normal ward diet. Faeces were not analysed for potassium, but the patient had no diarrhoea, and it is unlikely that significant amounts of potassium were lost by this route. Daily faecal loss measured for 83 days in four patients on high potassium intake and without diarrhoea has ranged from 3.25 mEq/day (mean 9.4 mEq).

The lowering of total red-cell and muscle potassium had been of the order of 25%, as shown by the amount of potassium retained.

The outstanding interest in this case was the occurrence of gross amino-aciduria, without glycosuria, during the period of potassium depletion (Tables I and

II). At this time also the early morning urine was of low and fixed specific gravity. After potassium repletion both these findings disappeared.

Denton, Wynn, McDonald, and Simon (1951) have reported two cases in which a similar amino-aciduria occurred during potassium depletion. Neither had glycosuria. In one of their two patients' treatment with potassium abolished the amino-aciduria; the other patient died while still depleted of potassium.

In his recent review Stanbury (1958) draws attention to the fact that amino-aciduria has resulted from severe and acquired renal tubular disturbances and that it has on occasion been reversible. We feel that the amino-aciduria in our patient was caused by a renal tubular disturbance for which the potassium deficiency was responsible. This interpretation is supported by the normal liver-function tests, by the low and fixed specific gravity of the urine at the time of amino-aciduria, and by the disappearance of the urinary abnormalities on correction of the potassium depletion. In the patient with nephrotic syndrome and both amino-aciduria and potassium depletion, reported by Stanbury and Macaulay (1957), treatment with potassium had no effect on the amino-aciduria. In their patient potassium depletion had been present for much longer than in our patient or those reported by Denton *et al.* (1951).

It is submitted that the possibility of potassium depletion and/or intracellular acidosis should be considered in every case of amino-aciduria and also that amino-aciduria should be looked for when potassium depletion is suspected.

Summary

A case is presented in which potassium depletion was accompanied by significant amino-aciduria, which disappeared with potassium therapy.

Attention is also drawn to the difficulties attendant upon a definitive diagnosis of potassium depletion, and it is again emphasized that normal serum potassium levels can be misleading.

Possible implications of the findings are discussed.

Thanks are due to Dr. J. D. Blainey (department of experimental pathology) for assessment of amino-aciduria, and to Drs. R. F. Crampton and D. Matthews (department of physiology) for help with the muscle biopsies. Other investigations were carried out by the department of biochemistry at the Queen Elizabeth Hospital.

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PROPHYLACTIC USE OF ORAL PENICILLIN IN RHEUMATIC FEVER, CHOREA, AND CARDITIS

BY

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We have attempted to show the actual occurrence of rheumatic manifestations, intercurrent respiratory infections, and laboratory evidence of streptococcal infection in children suffering from heart disease and given penicillin prophylactically. At the St. Joseph's Children's Heart Hospital, Rainhill, under the devoted care of nursing and teaching sisters, their treatment and progress have careful and close surveillance. Three physicians regularly attend the hospital, so that each child is usually seen once in the course of each week and more often when necessary. The 40 beds are occupied mainly by children suffering from rheumatic heart disease, but there are also a few children who have congenital heart lesions. No attempt at a statistical study or a comparison of the effects of penicillin V with penicillin G has been made because the series is too small.

For the first year of the trial prophylaxis had not been given and the results are analysed under the heading of "control period." In the second year penicillin V tablets, 60 mg. b.d., were used; these tablets were taken on an empty stomach with the sister present at the bedside. A similar procedure was followed throughout the third year, penicillin G tablets, 200,000 units b.d., replacing the penicillin V.

The clinical progress of each child was commented on independently by each physician. Throat swabs were taken from every child at fortnightly intervals, and these were cultured, typed, and grouped at the Royal Southern Hospital. The delay between taking the swab and culturing it was between one and a half and two hours, but we first proved to our own satisfaction that under the particular circumstances the streptococcus group A will survive for much longer periods than this.

Blood was also taken from every child at fortnightly intervals and estimations were made of the erythrocyte sedimentation rate and the anti-streptolysin O (A.S.O) content. With the kind co-operation of Distillers Company Ltd., the majority of specimens of blood were also forwarded to their laboratories, where the penicillin content was estimated.

Clinical Findings

TABLE I.—*Manifestations of Acute Rheumatism*

	No. of Cases	Rheumatic Fever	Chorea	Carditis	Total
Control period	38	5	3	0	8
Penicillin V ..	40	4	2	1	7
,, G ..	39	1	1	1	3

Rheumatic Fever

The cases of rheumatic fever occurring during the three years (Table I) were considered under two headings: group A, those who fit the Jones criteria (modified) as reported by the Royal College of Physicians (1957)—that is, showing two major or one major and two minor manifestations; and group B, those who, while not fulfilling the criteria, were considered to have rheumatic fever by three physicians who each saw the case independently.

Control Period.—During this phase there were three cases of group A type. One had been in hospital for some years, the others had been admitted 14 weeks and eight weeks previously, but as they were quiescent for some time before transfer from another hospital we regarded them as showing fresh infection and not as relapses. In addition, two cases were classified under group B, both of whom had been under our care for some months prior to the recrudescence.

Penicillin V Period.—One child had rheumatic fever of group A type as shown by fever, joint pains, pallor, malaise, and the appearance of a pericardial rub. This child had been well and in St. Joseph's for the previous 15 months. Three children had rheumatic fever of group B type. The first (J.B.) had been well for 18 months. She developed low-grade pyrexia, malaise, pallor, a raised A.S.O titre (1,250), and a raised E.S.R., the episode lasting four weeks. The second (K.M.) had been well for seven months. She developed fever, arthralgia, and swelling of one ankle-joint; three months later a relapse occurred with fever, occasional joint pains, sweating, and a raised E.S.R. The third (S.H.) had been well for six months. She had fever, erythema marginatum, pallor, sweating, a raised E.S.R., and a raised A.S.O. She remained in this state of ill-health for five months in all. Two further cases require brief mention at this point. Both of them were suspected of continuous low-grade activity throughout the year of observation, but their relapse had begun in the control period and we feel that, in view of the doubt about them, inclusion was not warranted in this analysis.

Penicillin G Period.—There was one case of rheumatic fever (group B). This patient (D.G.) had been well for 19 months. Her illness lasted for two and a half months, during which she was pyrexial and complained of vomiting, epistaxis, and joint pains. It should also be mentioned that shortly after the year's observation ended, and while the children were still on penicillin G, there was a further case of rheumatic fever (group A), but this has not been included in the present analysis.

Chorea

Control Period.—During this phase there were three cases of chorea.

Penicillin V Period.—Two cases of chorea occurred during this time. One child (B.O'C.) had been well for the previous 23 months and then developed moderately severe chorea which lasted for one month. The other (G.N.) had been admitted towards the end of the control period with chorea, which subsided shortly after admission. Three and a half months after the beginning of penicillin V he had a mild and short-lasting relapse.

Penicillin G Period.—A boy admitted during this period was well on admission. Two and a half months later he had a mild and short-lasting attack.

Rheumatic Carditis

For reasons given elsewhere (Chamberlain *et al.*, 1958) we have been in the habit of separating patients in whom the sole manifestation of rheumatic activity was carditis from those suffering from rheumatic fever or chorea with or without carditis. It is the former group with whom we are concerned in this section.

Control Period.—There were no cases during this year.

Penicillin V Period.—One child (V.H.) had been well for the previous 18 months. She had malaise, pallor, a rise in A.S.O titre, and an episode of congestive cardiac failure in the absence of any evidence of pulmonary infection or other cause for the failure.

Penicillin G Period.—One child (G.P.) had not had any active rheumatism in the previous two years, but had established aortic and mitral valvular disease. She had been in congestive failure seven months previously during a bout of bronchitis. She again developed congestive cardiac failure, this time accompanied by erythema marginatum and epistaxis and with no evidence of respiratory infection.

Intercurrent Infections

Respiratory infections, chiefly bronchitis, are prone to occur in children with established rheumatic heart disease, not uncommonly precipitating congestive cardiac failure, and sometimes death occurs in consequence. We therefore analysed the figures with regard to these episodes in the three years.

Control Period.—Six children had severe bronchitis—one child on three occasions, two on two occasions, and the remaining three only a single bout. Three of the children developed congestive failure, which we believe to have been precipitated by the bronchitis.

Penicillin V Period.—Six children had bouts of bronchitis, two of them having two attacks in the year. In two cases congestive cardiac failure appeared as a consequence of the illness. Two other children were in congestive failure when they developed superimposed bronchitis and so were extremely ill; fortunately both recovered in due course.

Penicillin G Period.—Three children had bronchitis—one child on two occasions. In two cases the attacks were mild and none of these children developed cardiac failure.

Special Investigations

Erythrocyte Sedimentation Rate.—Most of the children suffering from rheumatic fever, carditis, or bronchitis showed a rise in the E.S.R., but this was not an invariable finding. During the three years of our study several other children showed a prolonged and definite rise in the absence of any manifestation of rheumatism. It would thus seem that this investigation is of minor value only, and we have come to regard it as an unreliable guide in modifying the child's routine.

Throat Swabs.—Despite great care in taking, transmitting, and examining throat swabs a group A streptococcus (and this penicillin-resistant) was identified in only one child in the three years. This patient had satisfactory blood levels from penicillin G. On the other hand, many streptococci of other groups were isolated. Though complaint was often made of "sore throat," no typical case of tonsillitis was seen in the series.

TABLE II.—*A.S.O. Titres*

	October	November	December	January	February	March	April	May	June	July	August	September
Penicillin V Period, 1955–6												
M.H. ..												500
J.F. ..		250	350	250								250
T.R. ..											1,250	900
J.R. ..												500
E.R. ..				350	500	350			250	250	350	620
P.M. ..		350	500	250	350	620	620					
P.Me. ..					350	350	900	620				
G.T. ..			180	500	250							
Penicillin G Period, 1956–7												
M.H. ..	620	900	620	500	500	500	350					
J.F. ..	350	500	180	350	500	500	(Discharged)					
T.R. ..	900	900	620	620	900	500	500	350	620	620	(Discharged)	
J.R. ..	350	900	500	500	500	500	250					
E.R. ..	1,250	900	250									
F.M. ..								620	900	900	1,250	900
G.N. ..											500	620
S.H. ..	1,250	900	620	620	900	900	620	500	620	900	900	1,250
*G.W. ..	1,250	1,250	500	900	900	900	1,250	900	1,250	900	900	1,250
*J.D. ..	1,250	1,250	1,250	1,250	1,250	620	1,250	1,250	1,250	1,250	500	1,250
*D.J. ..	350			500	620	620	620	500	620	500	500	620

* These cases were not included in Table I, as they were suffering from active rheumatism on admission.

Anti-streptolysin O Titre.—Table I shows the number of children suffering from rheumatic fever, carditis, and chorea. These children have been omitted from Table II, as we wish to discuss the significance of an elevation of the A.S.O titre in the absence of any evidence of rheumatic activity. *Control Period:* Two children showed a rise in titre; in one case it varied from 500 to 620 for a period of eight months; in the other there was a rise to 350 for a period of two months.

Blood Penicillin Levels.—Since blood penicillin levels were estimated on all the children under observation at fortnightly intervals it is obviously impossible to reproduce all the figures here. We have therefore chosen at random the first four girls and the first four boys who were in St. Joseph's throughout the entire two-year period, and who are in fact representative of the remainder. By altering the time of giving the tablets and the times of taking blood we were able to obtain a guide to the varying level of the blood penicillin at different periods after taking the antibiotic. We have arranged Table III so that this is clearly shown rather

TABLE III.—*Blood Penicillin Levels in Units Per ml.*

	Dose-Sampling Time in Minutes							
	30	60	90	120	150	180	210	240
Penicillin V, 60 mg. Tablet								
J.R.	0	0·08	0·16	0·16	0·15	0·06		
E.R.		0·10	0·21	0·22	0·14	0·21	0·10	0
D.G.	0·021	0·23	0·24		0·09	0·07		0·04
V.H.	0	0	0·13		0·24	0·13	0·15	
B.O'C.		0·15		0·18	0·06	0·11	0·04	0·05
G.T.	0	0	0·17		0·13	0·07	0·02	
G.N.	0	0·23		0·19		0·15	0·06	0·05
P.N.	0	0·15			0·14	0·09	0·17	0·09
Penicillin G, 200,000 units Tablet								
J.R.	0·40	0·65	0·26	0·56	0·12			
E.R.			0·23	0·26	0·76	0·16		
D.G.	0·75	0·72	0·50	0·75	0·28	0·36		
V.H.		0·98	0·28	0·54				
B.O'C.			1·11	1·02	0·64	0·32	0·22	
P.N.		0·60	0·71	0·23	0·30			
G.T.			1·02	0·75	0·35	0·06		
G.N.			0·087	1·02	0·56	0·17	0·01	

than reproduce the figures week by week for each child over a period of two years. Naturally it has followed that over such a long period of observation each child would have his blood taken at the same number of minutes after his tablet on more than one occasion. The resultant blood levels were closely similar in the vast majority of such occasions, but when it has not been so we have calculated the mean level. The number of minutes between the taking of the tablet and the subsequent taking of blood is referred to as the dose-sampling time. For completeness a small number of children suffering from congenital heart disease were given penicillin V, 240 mg., and the blood levels so obtained were equivalent to those obtained with penicillin G, 200,000 units.

Discussion

Blood Penicillin Levels

Before discussing our clinical results it is necessary to consider whether the dosage of penicillin could be regarded as adequate. In a study of the prophylaxis of the recurrence of rheumatic fever (Kohn *et al.*, 1953) it was repeatedly found that the group A strains of the β haemolytic streptococcus were sensitive within the range of 0.001 to 0.08 Oxford unit of penicillin per ml., of these 80% were sensitive within the range of 0.01 to 0.02 unit.

Table III shows that, in the case of penicillin V a level much greater than 0.08 was reached in all cases between 60 and 90 minutes after taking the tablet, and was maintained for a minimum period of 90 minutes. Despite this, the clinical results were poor. In consequence, for the year of trial with penicillin G the dose was raised to 200,000 units b.d. With this dose the required blood level of 0.08 unit was reached within 30 to 60 minutes and maintained for longer than three hours in some cases; the maximum levels were also very much higher.

Since our study began, the Rheumatic Fever Committee of the Royal College of Physicians of London (1957) has suggested that oral penicillin G, 200,000 units b.d., or alternatively penicillin V, 120 mg., b.d., is effective when given over prolonged periods for the prevention of group A β haemolytic streptococcal infections in children and adults. Massell *et al.* (1957) suggest that oral buffered penicillin G, 200,000 units b.d., is effective, but that there is "still room for improvement of presently used regimes."

Clinical Findings

Previous literature has indicated that, in general, oral penicillin is effective in reducing the risk of relapse in rheumatic fever.

Pitt Evans (1950) used 100,000 units of calcium penicillin, given in 5% glucose, once daily before breakfast. This trial was carried out over two years on children admitted to a convalescent home for a maximal stay of six months, and they could not therefore be followed up long enough. There were no relapses of rheumatic fever in 155 cases, as against four in a control group.

Brick *et al.* (1950) used 50,000 units of oral penicillin twice daily in their 38 patients followed at monthly intervals for two years. Three had rheumatic recurrences as against six in a control series of the same number.

Kohn *et al.* (1953) gave their cases 200,000 units of oral penicillin four times a day for the first seven days of each month from October to June. In the third year of their study there were no relapses in 48 cases, in the fourth year one child relapsed out of 45 (this child had large infected tonsils), and in the fifth year one out of 40. Two other children also relapsed, but this was attributed to poor co-operation. Massell *et al.* (1957), using oral buffered penicillin, 200,000 units b.d., noted 2 relapses in 114 rheumatic subjects observed over 6,545 " patient weeks."

In our own series 7 children out of 40 relapsed within a year of prophylaxis with penicillin V. We have been unable to find a series in the literature with which to compare our results, but it is evident that, at least on the dose we used, they are unsatisfactory; we are at the moment continuing the trial on a schedule of 240 mg. b.d.

During the year on penicillin G, 3 children relapsed out of a total of 39, which might be taken as showing improvement on the two previous years, though it is not statistically significant. On the other hand, these results must be regarded as much less successful than those obtained by previous workers, and it is difficult to explain this discrepancy. It is conceivable that had our cases not been under close observation the case of chorea could have been missed, but this cannot be said of the other two, nor of the third child, whose relapse occurred shortly after the year under analysis. Whatever the reason, our figures leave no doubt that the schedule of treatment we used is clearly open to improvement.

An apparently more encouraging feature was the comparatively infrequent and mild bouts of chest infection occurring while the children were on penicillin G as compared with previous years.

Laboratory Evidence of Streptococcal Infection

Pitt Evans (1950) found that seven of the children receiving penicillin carried the group A streptococcus in the throat for two consecutive weeks and four for three consecutive weeks; there was one doubtful case of tonsillitis. None of the patients on penicillin showed a rise in A.S.O titre though these were estimated at monthly intervals.

Brick *et al.* (1950) took monthly throat swabs and obtained a single positive swab from each of three children.

Kohn *et al.* (1953) studied the organisms grown from the throat in detail. Unfortunately it is not clear how many of the 110 positive swabs in the fourth year and the 47 positive swabs in the fifth year were from the children on penicillin, and how many from the controls. They do, however, comment that they have observed positive cultures in young adults receiving from 100,000 to 600,000 units of penicillin daily. In no case did they find a penicillin-resistant organism. These workers did not undertake A.S.O studies.

Massell *et al.* (1957) prepared throat cultures and estimated the A.S.O titre every four weeks on each of the 114 rheumatic subjects attending their clinic and also at additional times when they attended these patients' homes in the event of illness. They regarded a positive culture or a rise in A.S.O titre as evidence of infection. In seven children these were accompanied by clinical manifestations in the throat, 19 others were asymptomatic; of these latter the rise in A.S.O titre was the only manifestation in seven.

Table II reveals that eight otherwise healthy children showed a marked rise in A.S.O titre during the year 1955–6, and that four of these maintained this rise for several months during the subsequent year. Three further children showed a rise in A.S.O titre in the year 1956–7, while three children admitted in this year maintained a high level for 12 months despite the early subsidence of any evidence of rheumatic activity.

Thus our figures bear a close resemblance to those of Massell *et al.*, though we were unable to support our findings with positive throat cultures except in one case.

Massell *et al.* have suggested from their work that it is unlikely that group C or G streptococci were responsible for the A.S.O rise in their patients. We were consistently unable to isolate group A streptococci from the throats of our patients before or during a period of rising titre of A.S.O, despite considerable effort.

In view of this it seems an open question whether the A.S.O rise in these cases was due to a streptococcus other than group A, or whether the group A streptococcus was harboured by the patient in some inaccessible region, and this despite penicillin prophylaxis.

If this latter suggestion is correct it would follow that children susceptible to rheumatic fever and carditis may harbour the streptococcus for a prolonged period and show antibody reaction to it without apparently suffering a relapse of their rheumatism. This would indicate that, in this phase, either some other requisite factor for the development of rheumatism is not present or some inhibiting factor is at work.

Summary

A study has been made of the prevention of manifestations of rheumatic disease in susceptible children by the use of penicillin V, 60 mg. b.d., and penicillin G, 200,000 units b.d. Neither regime proved completely effective. It is hoped that larger doses may prove more successful, and investigation along those lines is proceeding.

It has also been shown that many children on these prophylactic measures develop a high anti-streptolysin O titre in the absence of evidence of rheumatic disease, and the significance of this finding is discussed.

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ACCEPTANCE OF PSYCHIATRY BY THE MEDICAL STUDENT*

BY

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The attitudes which students acquire during their childhood, their school, and their preclinical training determine to a considerable extent their acceptance or rejection of psychiatry. But these attitudes are liable to reinforcement by their experience of clinical medicine and by their first contacts with psychiatry itself. It is difficult for the student to approach this subject with the same objectivity which he can give to other subjects. He is in danger of uncritical acceptance or of uncompromising rejection, and either attitude is equally undesirable. Many explanations have been offered for this. Among them is the fact that in most schools psychology and sociology are not taught adequately in the preclinical period and the place of psychiatry in the curriculum is relatively small.

Moreover, when psychology has been taught, it is not infrequently of the dry-as-dust academic variety, which the student cannot relate to the personal problems he meets in his patients and in everyday life. There is then the alleged hostility to psychiatry of clinical teachers in other fields of medicine and the undoubted tendency of the young student to identify himself with the attitudes of those whom he admires and respects. An excessive emphasis on psychopathology and on psychological determinism has also been blamed; for this is foreign to his thinking, and the impact, if it is felt at all, arouses anxiety in the student himself. More significant perhaps is the fact that there is as yet no body relevant to aetiology and treatment which is generally acceptable and accepted. Psychiatry is still cloven by the false antitheses of the psychosocial and organic approaches to the subject.

Teleological Aspect of Behaviour

No doubt all these and many other reasons play their part in shaping the student's attitudes. It is suggested, however, that the basic reasons lie deeper and are related to the explanatory hypotheses which each of us must hold about the nature of man and about his behaviour. For 150 years biological science, and hence medicine, has tried to reach understanding of living phenomena in terms of physics and chemistry. A strict aetiology has implied a search for physical causation for all forms of disease and behaviour. The great successes of the anatomico-pathological concept of disease has abolished teleological explanations for biological events. Every event in nature is viewed retrospectively in terms of a chain or net of causative factors which determined it. Every endeavour has been made to narrow the concept of biology as science to the causal-mechanical methods of physics. It is indeed only reasonable and profitable to think about the functions and dysfunctions of a tissue, an organ, or an organ-system in terms of aetiological causation, but it has never been possible to think of human behaviour at its most integrated level in these terms. Indeed, it is only possible to do so when the concept of purpose or teleology is invoked.

We cannot avoid this forward-looking teleological aspect of behaviour, and this, which has been so unpopular and almost heretical among scientists, has raised the cry that psychiatry is "not scientific." Yet in the development of science teleological explanation probably always precedes and provides the ground for the discovery of causal mechanisms. It is a necessary stage in the development of science, and it is not intrinsically "unscientific." Indeed, science is every logical connexion of facts in thought whether it is aetiological or teleological.

The modern medical student, in contrast to his predecessors in other centuries, is little burdened by philosophy. He has escaped from preoccupation with mediaeval dualism—the mind–body problem—but he shares the prejudices of his cultural setting and he dislikes doubt and uncertainty. He is offered an immense array of technical knowledge, but he needs above all a satisfactory *explanatory hypothesis* about human behaviour with which he can work and into which he may fit, as best he can, all the data of human disease and disorder which he will meet. The great successes of aetiological medicine in the present century, based on the explanatory hypothesis of biology, are plain to all and are accepted without question. The failure of this hypothesis to cover all the facts of human behaviour and particularly those of psychological illness is, however, the threat which the student meets as soon as he encounters his first patients.

Determinism

The chief explanatory hypothesis of medicine rests upon physical determinism, the logic of which is that all physical events in the universe, and in the case of medicine human diseases, are determined by a necessary antecedent chain of physical causation. Physical determinism, however, while it is an entirely satisfactory explanatory hypothesis for biology, for macrophysics, and for much of medicine, is not so when it is applied to either normal or abnormal human behaviour. Strictly speaking, physical determinism is mechanism, and logically means that every event, including human behaviour, is completely explicable in terms of its antecedents. Thus, given complete knowledge of conditions, one would have complete knowledge of precisely how a person will, indeed *must*, act. The

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implications of this for religion and for the notion of free-will are obvious.

Thus many doctors, nurtured throughout their school and undergraduate careers on an aetiological explanatory hypothesis about the nature of disease based on physical determinism, share with their teachers a great reluctance even to think about human behaviour, human feelings, motives, and desires, in the same terms. This difficulty would not be so great if, when the attempt to transfer the explanatory hypotheses of medicine to mental illness was made, it was found that human behaviour, both normal and abnormal, could be "understood" in terms of a respectable chain of physiological and biochemical events. But the phenomena of mind and of mental illness cannot as yet be "explained" within any system of physical determinism. In its place the student is offered, rather late in his training, a variety of other explanatory hypotheses which are foreign to his thinking and to his conceptions of the nature of disease. In the main these are hypotheses based either on psychological determinism or on cultural determinism, and both include teleological ways of thinking.

This is not the place nor the time to defend teleology and its place in science. It is, however, surely prejudice to hold that only causal connexions are the proper objects of science. Yet the evils of exclusive preoccupation with either causal or purposive connexions are easy to see. On the one hand the organic-causal hypothesis of medicine has resulted in a situation where, from its exclusive use, nearly half the ills of man remain outside consideration. On the other hand a preoccupation with psychological determinism has led to psychoanalysis, and that, with cultural determinism, to Marxism. Any explanatory hypothesis, exclusively taught and exclusively believed, leads to a "total ideology," which has the imprint of religious faith. Once a total ideology has been acquired there is little room for manœuvre or for progress.

Ultimate Object of Study in Medicine

The spectacular success of the application of the physical sciences to the problems of biology and medicine have had, as Woodger (1956) points out, an adverse effect on the psychological and social sciences. This is apparent in the medical curriculum. One function of education is to extend the range of the student's knowledge of reality and of his power to control it. The ultimate object of study in medicine is the patient himself, not a piece of him, such as his kidneys or his respiratory system. It is obvious that physics and chemistry can be taught only in a laboratory and a class-room, and the objects of study must be materials. Anatomy and physiology, which pertain to the living, are also taught in the laboratory, and the materials are the cadaver, the test-tube, and the recording apparatus. It is only late in the third year that the student meets the real object of his studies—the living patient. Even then his attention is constantly directed not to the patient himself but to parts of him. Despite much lip-service in favour of treating the patient as a whole, this is rarely the case—and this is inevitable, since the teachers are themselves specialists in different branches of medicine, and are experts in the physico-chemical mechanisms underlying disease processes in particular organs and systems. The indoctrination in aetiological processes, exclusively accepted as the only reality of medical science by his teachers, starts in the student's school and is perpetuated throughout his preclinical and clinical training. The search for the biochemical or structural lesion remains the exclusive object of clinical inquiry.

Medical education is not without its pains and its anxieties. The realities of disease and death are themselves painful and often shocking. We have all accepted the traumata of the dissecting-room, the operating theatre, the inevitable deaths, and the necropsy room. But the student's gradual introduction to these painful aspects of medical reality is cushioned for him by his progressive acceptance of the explanatory hypothesis of disease processes and the intrinsic interest in the subject. From this observation of human disease in the framework of the hypothesis, he himself, as well as the patient as an individual, can remain outside. The reality of psychological illness is also painful, and the recognition of the influence of emotional factors in suffering causes anxiety because it is something from which the patient as an individual, and the student as a fellow human being, cannot be excluded. Attempts to do so by ridicule or by denial are commonly seen. Nothing that the student has met during his previous experience of medicine as applied science fits him to meet this stress. Indeed, as this paper has tried to show, the body of knowledge and of concepts which make up his explanatory hypothesis about man have been, it would seem, almost expressly designed to shield him from awareness of the patient as an individual.

There is no easy answer to this. Perhaps the very success of the traditional organic approach to causation will in time draw attention to the large area of ignorance as opposed to what is known. Rearrangement of the medical curriculum and a larger and more extensive representation of psychiatry in it have been advocated by many, and most particularly the introduction of formal teaching of psychology and sociology in the preclinical period. A fundamental change in the climate of opinion must, however, be awaited. Until the limitations of the explanatory hypotheses of a medicine based on causal-mechanistic concepts is more generally recognized, little change can be expected. Such recognition would lead to a reformulation of the roles of causation and teleology in human behaviour, and to the idea that physical determinism, while necessary to all understanding of the mechanisms of bodily functions, does not provide the techniques for elucidating and controlling human behaviour. When this is accepted it is probable that the student will not have to wait three years before he meets the object of his studies—namely, the whole individual. For it can be argued that every science can be taught only through practical experience of the object of that science.

The capacity for making observations on individuals can be acquired only when individuals are available for study. Introduction to the realities of psychological life should therefore start at the beginning of the student's experience, not as a theoretical subject heard about only in lectures, but as a practical exercise in the nursery and school, in the home and factory, in the prison and geriatric unit.

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TUMOURS OF THE HAND*

BY

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The small number of papers published on the incidence of hand tumours, mostly from America, differ considerably, and suggest that selection has varied according to the specialized units in which the authors worked. For example, Mason (1954) gives a high incidence of malignant tumours, whereas the clinical impression in this country was that malignant tumours of the hand were uncommon. Therefore it was thought that it would be of value to analyse a series of hand tumours in order to make a practical estimation of the proportion of each type.

This paper is based on an analysis of 300 tumours of the hand presenting consecutively over a period of three and a quarter years in a casualty and an orthopaedic department of a big general hospital. All localized swellings that occurred below the level of the radio-carpal joint are included as being in the hand. Warts alone have been excluded, since these cases were usually sent direct to the skin department.

Of the 300 cases 61% were ganglia of various types, 10% were epidermoid cysts, and 29% comprised no fewer than 27 other diagnoses (see Table). There were 46 neoplasms (44 benign and 2 malignant), one secondary chondrosarcoma, and one melanoma.

Tumours of the Hand. 300 *Consecutive Cases*

Type	1st 100	2nd 100	3rd 100	Total
Ganglion of carpus	39	41	42	122
,, ,, hand	16	23	22	61
Epidermoid cyst	13	7	9	29
Tumour of skin	7	1	4	12
Fibroma	1	1	1	3
Melanoma	1	—	—	1
Mucous cyst	1	—	1	2
Secondary neoplasm	1	—	—	1
Xanthofibroma	1	—	—	1
Papilloma	2	—	—	2
Sebaceous cyst	—	—	2	2
Subcutaneous tumour: Lipoma	4	—	1	5
Tumour of tendon sheath	5	3	2	10
Synovioma	5	3	1	9
Fibroma	—	—	1	1
Tumour of vessels	3	4	2	9
Haemangioma	1	3	2	6
Traumatic aneurysm	1	—	—	1
Organized haematoma	1	—	—	1
Thrombophlebitis migrans	—	1	—	1
Tumour of nerve	2	5	1	8
Neurofibroma	1	2	—	3
Neurinoma (neurilemmoma)	—	2	1	3
Stump neuroma	1	1	—	2
Tumour of bone	4	5	6	15
Enchondroma	1	1	4	6
Osteochondroma (and exostosis)	3	1	1	5
Osteophyte	—	1	—	1
Multiple exostosis	—	2	1	3
Miscellaneous	7	11	11	29
Foreign body fibrosis	1	3	5	9
Pyogenic granuloma	—	2	4	6
Tenosynovitis	3	2	1	6
Dupuytren	1	2	—	3
Rheumatic nodule	1	2	1	4
Calcinosis	1	—	—	1

Some of the figures for individual tumours, analysed in the text, are based on more cases than occurred in the consecutive series of 300 cases.

*Read in the Section of Orthopaedics at the Joint Annual Meeting of the British Medical Association and the Canadian Medical Association, Edinburgh, 1959.

Ganglion

The common clinical features of the ganglion are too well known to need repetition. The figures in this series correspond closely with those given by Carp and Stout (1928). Women comprised 74.4%, the large majority of them aged between 15 and 45. The two main reasons why the patient reported were aching pain and the cosmetic appearance. Fear that the swelling is a cancer often causes the patient to seek advice.

There are five main types of ganglion in the wrist and the hand.

1. *Common Dorsal Ganglion of the Wrist.*—This usually overlies the dorsal carpal ligament opposite the proximal end of the capitate bone, on which there is a prominent tubercle. It arises from the ligament, and it is probable that the constant friction of this tubercle against the ligament has something to do with the frequency of the ganglion in this position. I have completely excised this ganglion in some cases by dissecting off the ligament and been successful in leaving the synovial membrane intact.

2. *Arising from Volar Ligament of Wrist-joint.*—In this position the ganglion is in close relation with the radial artery, which is often palpable running across the ganglion and sometimes causes it to be bilocular.

3. *So-called "Sesamoid" Ganglion.*—This is often mistaken for a sesamoid bone in association with the metacarpophalangeal joints. It arises in fact from the fibrous flexor tendon sheath, opposite the neck of the metacarpal or the middle of the shaft of the proximal phalanx. The sheath is firmer and inflexible here, whereas over the joints it is much more lax since it has to fold up in flexion. The ganglia arise from the rigid parts of the sheaths. It is possible that they are caused by pressure damage, as I developed several after lifting a heavy radiator with a sharp edge. If they persist and cause symptoms the only treatment is excision.

4. *Ganglia Arising in Association with Tendons and Joints on Dorsum of Fingers.*—These are often lobulated and occasionally fibrous.

5. *Ganglia Arising in Tendons.*—These occur in cases of rheumatoid arthritis, by degeneration in the tendons.

Many theories on the origin of ganglia have been advanced. Ledderhose (1893) put forward the most widely accepted view that they arise by degenerative changes in the connective tissue around the joints and tendon sheaths. King (1932), of Melbourne, agrees closely with this idea, except that he regards the contents as a mucinous secretion. De Orsay *et al.* (1937) of Philadelphia, do not accept this latter view, as they state that the chemical nature of the contents corresponds more closely to a degenerative myxoid material.

Microscopically, the ganglion shows compressed fibrous tissue, without epithelial lining, containing myxoid material. Those ganglia which show their origin most clearly are the sesamoid type arising from the flexor tendon sheaths, as the whole lesion can be seen and the ganglion can be excised intact with the fibrous tissue from which it arises. My view is that these ganglia arise by degeneration from the fibrous tissue of the joint capsules and the flexor tendon sheaths, and it is probable that this degeneration is initiated by trauma or overuse.

Epidermoid Cyst

Of the 300 tumours, 29 were post-traumatic epidermoid cysts. A total of 38 have been seen. These cysts are usually spherical, but are sometimes ovoid or even lobulated. They lie close beneath the skin, almost always on the palmar surface of the hand or fingers. They are often tethered to the skin at the site of the scar of the injury by which they have arisen. They are usually very firm, and fluctuation is not easy to elicit. Very slight pressure on or near the cyst causes the exposed surface to blanch, giving the overlying skin an intense whiteness.

Epidermoid cysts are clearly related to injury. A scar overlying the cyst can commonly be found: 20 patients out of 23 with a clear history related it to a specific injury. The lesions occur in persons whose work renders them liable to injury or in those who have had a laceration or a perforating or crushing injury.

The average age of these patients was 43. The age distribution shows a great preponderance of those of working age. One boy of 9 years had a definite history of having cut himself several years before.

The sex incidence is interesting. King (1933) reported only 3 out of 16 in females, suggesting that this distribution was also subsidiary to trauma. In the present series 13 out of 38 were in females. The change can be explained by the great increase in the number of women in industry since 1933.

Another well-marked feature is the latent period in most cases between the injury and the observation of the cyst. This is commonly months, but may be years.

Macroscopically, the cyst has a tough wall about 1 to 2 mm. thick. This wall is intensely white. The contents resemble the material in a sebaceous cyst, except that they are less greasy and more gritty and have a crystalline sheen.

Microscopically, the wall is surrounded by compressed fibrous tissue. The wall itself consists of squamous epithelium without papillae, and with laminated keratin within it. In the centre is the soft material which is about half protein and about half cholesterol, with small amounts of fat and fatty acids.

The cyst may rupture and discharge its contents, but the opening will heal over again and the cyst refill. Infection is a fairly common complication, seen three times in this series. Sometimes the distal phalanx is involved, with erosion of bone.

It is generally accepted that this lesion is due to implantation of some part of the skin in the subcutaneous tissues. Whole skin is not thought to be the likely cause, as the experimental evidence indicates that such an implantation would cause a much more rapid formation of the cyst. King (1933) notes that there is always a layer of connective tissue between the cyst and the skin, and he postulates that the epithelium would have to be driven in a considerable distance to produce a cyst at this depth. In view of this, and the frequency with which a history of open or perforating injury is absent, he inclines to the view that the cyst may well be due to the epithelization of a haematoma or inflammatory focus by cells from a sudoriferous gland lying in the connective tissue below the skin, and involved in the damage. The epithelization may take some time to start, and this may explain the latent period.

Synovioma

The benign giant-cell synovioma of tendon sheath is to me the most fascinating tumour that occurs in the hand. It is also the commonest true neoplasm, though some people doubt its neoplastic origin. There are certainly some features about its natural history and its pathology that are intriguing.

Confusion has arisen in the past because some authors, particularly in America, call this tumour the xanthoma. In this country that name is reserved for the xantho-fibromatous deposits which occur in conjunction with a high blood cholesterol in cases of xanthomatosis.

Nine of these tumours were in the series of 300 under review, but there were 16 altogether in the hospital between 1951 and 1956. The lesion occurs in other places also, notably the foot and the prepatellar bursa. It is most common in women. In our series of 16 there were 14 women and 2 men.

The average age at onset was 34 years, and the average duration of the tumours before attendance for surgery was four and a half years. By definition they occur only in synovium—that is, near joints and tendon sheaths. In this series they were associated with tendon sheaths on the volar surface and joints on the dorsal surface of the digits. They vary in size from a few millimetres to 4 cm. in diameter and nearly always are smoothly lobulated with a definite edge. They spread locally along fascial planes and may extend into tendon or bone. Often they are horseshoe-shaped, lying deep to tendons, and encircling the phalanx. In consistency they are a soft solid, often misdiagnosed as cystic because of mobility. Pain is never severe, though they are often tender. As a rule they grow very slowly, but two of the patients were quite insistent that they appeared suddenly after an injury.

Synoviomas are soft greyish blue in colour and usually show red and yellow areas on both cut and uncut surfaces. The lobules are encapsulated separately, but not the tumour as a whole. The lobules burrow widely, and may extend into bone, into tendons, or almost encircle the finger deep to the tendons or under the skin. Digital nerves are often found in close proximity to the tumour. These relationships lead to difficulties at operation, and as a result small pieces of the tumour may be left behind and lead to recurrences.

This complication is reported in up to 40% of cases. Five of the 16 cases in this series had recurrences after the first operation. Microscopically, the synovioma is a partly encapsulated lobulated tumour, the bulk of which consists of greyish-white spheroidal-celled mesenchyme, intersected by collagen trabeculae of varying thickness. Nuclear pleomorphism is present, probably due to developing fibroblasts. Also a variable number of mitoses are seen, though generally very few.

The characteristic multinucleate giant cells resemble clumped cells of the surrounding mesenchyme. Another characteristic feature of this tumour is the synovial cleft, which has no epithelial lining. These are always present and are not artifacts. They are thought to represent an attempt by the tumour to reproduce synovial tissue.

The reddish areas of the tumour contain variable amounts of blood and haemosiderin. It is thought that they arise from minor trauma to the tumour and subsequent phagocytosis.

Large groups of foam cells are found. These are responsible for the yellow areas in the tumour and also for the name xanthoma, which is often given to it. Stewart (1948), Wright (1951), and Willis (1953), are all convinced of the neoplastic nature of the lesion, and reject the suggestion that it is inflammatory.

Malignant Synovioma

There were no cases of malignant synovioma in the series, but I have seen two since then—one by the courtesy of Mr. G. R. Fisk. The hand is a frequent site for this not very common tumour.

A coloured seaman presented with a diffuse swelling in the palm of the hand and extensions up the lumbrical canals on to the dorsum of the fingers. There was a history of recent injury at sea, and also an operation 12 years previously in West Africa. At operation I found pale-yellow granular material infiltrating the whole palm of the hand. Radiotherapy was given and the swelling disappeared after a few weeks. The hand was a little fibrosed but useful; there was no recurrence after one year.

This tumour usually metastasizes to the lungs eventually, but very seldom to lymphatic nodes.

In Fisk's case a gland was felt in the axilla, at another hospital, and a block dissection carried out. No malignancy could be found in the specimen. This tumour recurred about three years after irradiation and amputation was performed.

As there is not space to discuss all the tumours at length, I shall mention only points of interest.

Skin Tumours

Mucous Cyst or Myxomatous Cutaneous Cyst.—The so-called mucous cysts are curious lesions, most of which arise on the fingers, in close proximity to the base of the nail. The great majority occur in women of 45–60. They are rarely seen in males. They are 4 to 12 mm. in diameter, with a thin translucent covering, and contain syrupy fluid. The outstanding clinical feature is the frequency with which they recur after all forms of treatment except irradiation or radical excision followed by skin-grafting. Gross (1937) has pointed out that they arise by myxomatous degeneration of the corium.

Sebaceous Cyst.—This is very rare on the hand, and can occur only on the dorsum, in the hair-bearing areas, as there are no sebaceous glands on the volar surface.

Subcutaneous Tumour

Lipoma is not as common in the hand as elsewhere in the body, and is very rarely diagnosed pre-operatively, as the relative firmness of the skin and fascia in the hand modify the normal characteristics. Lipomata are classified by their situation. One subcutaneous lipoma was so tense that it was thought to be a sebaceous cyst.

Subfascial lipomata are divided into epivaginal and endovaginal, and it is in this situation that the so-called lipoma arborescens is found. Though not truly infiltrative, this type spreads along the fascial planes, expanding when the fascia is lax. They require wide exposure and careful dissection, as they are apt to recur if not completely excised.

Vascular Tumours

The angiomata are difficult to classify exactly as they are so variable in their form, but there are three types that occur in the hand. Curiously enough, it is uncommon to see these tumours in the skin as birth-marks, most being of the subcutaneous variety.

The hamartoma is in effect an unorganized overgrowth of fully differentiated vessels. These are often diffuse and multiple, and it is extremely difficult to eradicate them. One patient attended with a severe infection of the finger, and was insistent that nothing be done about the tumour.

The capillary haemangioma is usually small and raspberry-like, and consists of an irregular meshwork of endothelium-lined channels, covered with thin epidermis and often pigmented. There is a type in which the cells undergo proliferation and which is called a compact or sclerosing haemangioma.

The cavernous haemangioma in the hand is usually an encapsulated lobulated bluish tumour, as opposed to its common form the port-wine stain. It consists of a spongy network of intercommunicating blood-spaces.

Glomus Tumour.—The normal neuro-myo-arterial glomus is a specialized anastomotic system whose function is to control the arteriovenous circulation in the digits and to regulate the local and general temperature of the body. The vast majority of these tumours ocur in the hands and feet, with a predilection for the nail-beds. Around the central anastomotic channels are grouped a mass of glomus cells, and from these the glomus tumour, or haemangiopericytoma, develops. These lesions are commonest in the nail-beds and in females. They are characterized by the severe pain that is felt in spasmodic attacks after pressure over the tumour, and with changes of temperature. Treatment is by excision, and they are reported to be very resistant to local analgesia.

Nerve-cell Tumours

There are three tumours of nerve-cell origin which occur commonly in the hand.

The fibrillary neuroma is the amputation-stump neuroma or the tumour arising in a nerve as a result of injury. It consists of overgrowth of all the elements of the nerve.

The neurilemmoma, perineural fibroma, or neurinoma, is believed to arise from the Schwann cells of the neurilemma. This lies in the course of a nerve, and the nerve bundles fan out over it but are not involved in the tumour. A longitudinal incision in the nerve sheath allows it to be shelled out completely. It is an ovoid or round tumour, well encapsulated, and often brown in colour. It can be symptomless or acutely tender. One of the cases was unusual in that the lesion was on the dorsum of the hand, and lay beneath a pigmented patch of skin. Microscopically these tumours resemble the fibroma with whorls of spindle cells, but the typical feature is the palisading or regimentation of the nuclei. Three cases reported by Jenkins (1952) had all undergone cystic degeneration, and Morus Jones (1953) has reported a cystic tumour arising from a metacarpal.

The neurofibroma occurs as a solitary tumour, or in association with von Recklinghausen's disease. In this tumour the nerve is involved in the process and there

may be considerable disturbance of function. All parts of the nerve can be recognized as contributors to the tumour process.

Tumours of Bone

There were six cases of enchondroma in the 300. Jaffe and Lichtenstein (1943) describe this tumour as the solitary benign enchondroma of bone. They emphasize that it must be distinguished from the osteochondroma (or solitary exostosis or ecchondrosis) and also from Ollier's disease, in which there are multiple lesions. It is the commonest bone tumour in the hand.

There were 10 cases of this tumour in all. Six were in males, and eight were in the left hand. All were in phalanges (one in T.P., five in M.P., three in P.P., and one multiple). The average age of the patients was 33, spread fairly evenly from 5 to 57. Five males and one female attended with a pathological fracture after a minor injury. Three females and one male sought treatment because of a tender swelling. Eight of the 10 cases were treated by surgery with curettage, and most were packed with bone chips, though two were left unpacked following Mason's (1954) advice that the small ones heal quite adequately by ossification of the haematoma that develops in the cavity.

It is surprising how much of the rice-grain-like cartilaginous material can be curetted out of these tumours. It is advised that in order to prevent a recurrence none should be left, and some authors suggest that the cavity should be washed out with iodine or some other medicament for the same reason.

The *x*-ray appearance is of a translucent area in the shaft of the phalanx. It is usually lobulated, with some trabeculation, and occasionally there are areas of ossification within the tumour. Frequently a pathological fracture is present. There is wide acceptance of the theory that they are congenital in origin, arising from cell-rests.

The lesion always starts in the metaphysis, and does not spread to the epiphysis unless the patient is fully grown.

The cortex of the shaft is thinned and often expanded. The diagnosis from osteoclastoma would be difficult were not that tumour so very rare in the hand. When it does occur it is usually in the metacarpals.

The fragments examined microscopically usually show cartilage with mature-looking cells and much mucoid degeneration of the ground substance. The cells are regular and without conspicuous mitoses. Occasionally there are areas of ossification.

Tumour-forming Entities

Pyogenic Granuloma.—This interesting clinical entity is commoner than at one time thought. It occurs most often on the volar surface of the hand and fingers, where the skin is much thicker than elsewhere. It arises when infection follows an injury in which there is some loss of skin, or in which skin apposition is not obtained or is prevented by infection.

A granulation grows through the opening in the skin and spreads out like a mushroom above it. Epithelization cannot occur. Daily application of silver nitrate progressively reduces the size of the granulation and deals with the associated infection, and epithelization occurs across the wound when the granulations are reduced below skin level.

Summary

Few series of figures for the incidence of tumours of the hand have been published, and the proportion of malignancies in some of them appeared to be unduly high.

300 consecutive swellings in the hand seen in a casualty and orthopaedic unit of a big general hospital are analysed here to give an estimate of the proportions in which these tumours appear.

61% were ganglia, 10% epidermoid cysts, and all the remainder—27 different diagnoses in all—made up 29%.

There were 46 neoplasms, of which only two were malignant.

Salient clinical features and points of diagnosis of the various tumours are discussed and their relative frequency is indicated.

The treatment of most of these tumours is by excision, and the ideal condition for this is with a tourniquet under general anaesthesia.

My thanks are due to Mr. J. G. Bonnin, who suggested this study, and to Mr. R. G. Pulvertaft for much helpful advice.

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PHYSICAL ACTIVITY OF PATIENTS AFTER THE ONSET OF ACUTE CARDIAC INFARCTION

BY

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Complete physical rest is commonly held to be the guiding principle in the treatment of acute myocardial infarction (Miller, 1942; White, 1944; Scherf and Boyd, 1947; Friedberg, 1949; Blumgart, 1955; Levine, 1958). The slightest physical exertion in these cases is regarded as potentially lethal. But does the person with an acute myocardial infarct in fact do what he should? It is often found that an attack is immediately followed by a state of marked restlessness in the patient, associated with severe pain. He cannot remain quiet in bed, but tends to move or even gets up and walks about the room in his agony (Warburg, 1943; McLeod, 1949).

The object of this paper is to present my observations on the activities, and especially the physical exertions, of patients with acute myocardial infarction from the onset of the attack to the time when medical aid was sought.

Material

The series consisted of 102 men and 31 women, all from Helsinki, admitted to the emergency ward of the Maria Hospital in 1957. Their activities from the onset of the acute myocardial infarct to the time when they first received medical aid could be ascertained in full detail. The series included only clinically frank cases of acute myocardial infarction with typical signs of severe pain. Further criteria for inclusion in the series were distinct changes in the electrocardiogram, an elevated white blood count, and a definite rise in the glutamic serum transaminase (S.G.O.T.) value, in the erythrocyte sedimentation rate, and in the temperature. A few cases, however, were included though they did not fill all the above criteria. In these the presence of a massive acute myocardial infarct was ascertained by other means—for instance, by necropsy in fatal cases.

The average age of the 102 men in the present series was 51.4 years, the youngest being 36 and the oldest 81. Ten of these died during the first week in hospital and eight during the subsequent five weeks (from the second to the sixth week in hospital). Necropsy was performed on 17.

The average age of the 31 women in the series was 62.0 years, the youngest being 35 and the oldest 88. Seven of the women died during the first week in hospital and two during the subsequent five weeks. Necropsy was performed on eight.

Activity After the Attack

In studying the histories the first point established was the distance that the patient with an acute myocardial infarct walked before seeking medical aid. The group of patients who walked the shortest distance (0–20 m.) comprised also those in whom the infarct produced a state of restlessness that made them pace about the room, visit the lavatory, and so on. In many of these cases the total distance walked must have exceeded 20 m., but an accurate assessment could not be reached. The results are given in Table I.

The time of stopping work was ascertained in all those cases in which the patient had an attack while at work. Of the 38 men who were at work, 21 stopped immediately at the onset of the attack. But in spite of the pain 17 continued working (either without a pause or after resting a moment) for at least one hour after the onset of the attack. Nine of them continued at work till the end of the day, and two even returned to work on the following day. Of the 17 men who continued working, five became so weak as to be unable to move and were therefore taken direct to the Maria Hospital, five went to the doctor or the hospital unaided, and seven went home first and later consulted a physician or visited the hospital.

TABLE I.—*Distance Walked by Patients with Acute Myocardial Infarction Before Recourse to Medical Aid*

Distance in Metres	Men			Women		
	Under 60	Over 60	Total	Under 60	Over 60	Total
0–20	15	14	29	5	19	24
20–50	8	5	13	1	3	4
50–100	10	3	13	1	—	1
100–500	12	10	22	1	1	2
500–1,000 ..	11	3	14	—	—	—
Over 1,000 ..	9	2	11	—	—	—
No. of cases ..	65	37	102	8	23	31

Of the women, seven were working away from home when the attack occurred. All of them stopped work at once.

Forty-seven of the men were at home at the onset of the attack, and in 24 cases a physician was called to the patient's home, while 23 patients went to consult a doctor or sought advice at the medical out-patient department of the Maria Hospital.

Eighteen of the women were at home when the attack occurred, and in 15 cases a physician was called to the patient's home, while three patients went to the hospital for aid.

Fifty-five men had an attack away from home, and in only three cases was a physician called to see the patient where the attack occurred. In eight cases the myocardial infarct was accompanied by severe shock, so that the patient was unable to stand up and was therefore taken to hospital. Nine men went at once to consult a doctor or to visit the out-patient department of the Maria Hospital. Another group of 18 men went home immediately after the onset of the attack, and in eight of these cases a physician was later called to the patient, whereas the remaining 10 left home again to consult a private practitioner or to go to hospital.

Thirteen woman had an attack away from home. In two cases a doctor was called to the patient. Five of the women were unable to move on account of shock, and were taken to hospital. The remaining six went to hospital unaided.

Table II shows how the patients made their way to the medical attendant. The time that elapsed from the onset of acute myocardial infarction to the first recourse to medical assistance is shown in Table III.

TABLE II.—*Mode of Proceeding to the Medical Attendant in Cases of Acute Myocardial Infarction*

	Men	Women
Patient walked or went part of way on foot, part by bus or tram	48	2
Patient went by car, driving himself ..	2	—
,, was taken by car or taxi	20	7
,, ,, ,, ,, ambulance ..	5	5
Physician was called to patient	27	17
Total No. of cases	102	31

TABLE III.—*Time From the Onset of Acute Myocardial Infarction to Medical Attention*

Time in Hours	Men	Women
Under 3	57	25
3–6	18	3
6–12	6	2
12–24	9	1
Over 24	12	—

Discussion

The results of this investigation show that men did not, as a rule, take a rest immediately after the onset of acute myocardial infarction—as they should have done—but in spite of intense pain in the chest as many as 72% kept moving, and some of them walked long distances. Only 29 out of 102 ceased all activity at the onset of the attack: in 14 this cessation was due to shock and collapse—three of these patients fainted, and in one case the fall caused fracture of the skull. Thus in fact only 15 out of the 102 men deliberately took the right measures under the compulsion of the chest pain which accompanied the myocardial infarct. As the results show (Table I), there was no great difference between men over 60 and those under 60 years of age.

But the older men seemed to defy pain perhaps even more than the young. The women, on the other hand, differed radically from men in their response to the pain, for most of them (24 out of 31) stopped physical activity immediately the attack began.

The group of men contained numerous cases in which the total disregard of the condition, even when the patient was aware of the danger to life, appears incomprehensible. Mustering all his will-power, the patient continued to be physically active in spite of the relentlessly crushing pain in the chest and a sustained fight against loss of consciousness. Such an attitude is illustrated by the following two typical case histories.

Case 1.—A foreman aged 52 was cycling to his work. On the way he had a race with a youth, and by accident rode into the back wheel of his rival, so that he fell and the bicycle was damaged. As he was pushing his damaged bicycle he had a sudden attack of intense pain in the chest. Though he was hardly able to stand on his feet, he refused the help offered by passers-by, and instead of leaving his bicycle he struggled along, pushing it all the way to his workplace, a distance of about 1 km. In the courtyard his vision became blurred and he sank down to a sitting position. Other workmen saw this and helped him in, but he lost consciousness in the lift. He was taken to hospital by car. Examination revealed a myocardial infarct in the posterior wall. His recovery was uneventful. He admitted afterwards that he had never before experienced such severe pain as he had during the attack.

Case 2.—A blacksmith aged 72, who had been treated for myocardial infarction about a year before, had a severe attack of pain in the chest while at work at the forge. The pain was so intense that it brought him down to his knees. The foreman hurried to help him and proposed to take him to hospital by car. This offer, as he admitted later, annoyed him a great deal, especially as he did not particularly like his superior. He struggled to his feet saying that he could get to the hospital on his own feet and was in no need of the "carriages of grand folks." He left the forge on foot, but did not go to the hospital; instead, he walked home, a distance of about 1 km. On several occasions he was forced to sit down on a step or lean against a wall when the pain in the chest drained all strength from his legs and blurred his vision. At home the pain remained intense. At the insistence of his wife he went to the doctor in the afternoon. Even then he went on foot (about 300 m.). The physician sent him at once to the hospital by taxi. The electrocardiogram showed changes typical of posterior-wall infarction (S.G.O.T. was 335 units on admission). He died in hospital three weeks later.

A surprising point in Case 2 is that, though the patient had had a serious myocardial infarct a year before, he appeared to be none the wiser. A similar observation was made in other cases. In all, 29 men had had a previous myocardial infarct, and coronary insufficiency had been diagnosed in 19 others. Only 13 out of these 48 men who should have been aware of the serious implications of the pain in the chest took appropriate measures at the onset of the attack. Of the rest, eight walked 20–50 m., five walked 50–100 m., 14 walked 100–500 m., four walked 0.5–1 km., and another four walked over 1 km. This might lead to the conclusion that little can be gained by instructing patients, but some of them said later that they had not known how dangerous all effort was in that condition.

Among the men who were at work at the time of the attack there were 12 in whom damage to the coronary artery had been previously diagnosed or who had had a previous myocardial infarct. But only six of these stopped work at the onset of the attack, whereas the other six tenaciously kept on for at least an hour.

Among the men who went on with their work in spite of the attack, five were later forced to stop on account of shock, which was so severe that they could not remain standing, however hard they tried. The following is an example of such extraordinary endurance.

Case 3.—An electrician aged 47 had a severe attack of pain while at work. Bathed in cold sweat, he sank to the floor, but a short rest revived him. He then resumed work and kept on till the end of the workday (for about four hours) as he considered that the factory could not manage without him. From time to time he had to sit down because of faintness. After work he walked home. In the afternoon —it was a Saturday—the pain subsided. He spent the Sunday in bed, and as a dull ache persisted he decided to go to hospital next day. But he considered it his duty to go first to the factory to arrange a substitute for himself, thinking that the running of the factory might otherwise be endangered. He stayed at work for four hours on Monday morning, with the pain increasing again. After handing over to his substitute, he made his way to the hospital, partly by tram, partly on foot. Electrocardiography showed extensive changes characteristic of myocardial infarct. The state of shock in which he was admitted could not be totally rectified. He died about 40 hours later. Necropsy confirmed the diagnosis of extensive posterior-wall infarct.

The response of the women to the pain was entirely different from that of the men. All the women who were at work stopped working at once after the onset of myocardial infarction.

The mode by which they proceeded to the doctor or the hospital also reflects the men's defiance of pain. Here again the women took a much more realistic view. It seems almost incredible that, regardless of the intense pain caused by the myocardial infarct, nearly half of the men (48 out of 102) walked all the way to the medical attendant or went partly on foot and partly by bus or tram. In most cases this was obviously not due to lack of money, for on inquiry most of these men explained that as they usually moved about town on foot they saw no reason for departing from their habit.

McLeod (1949) found that many of the 28 American patients with acute myocardial infarction walked a shorter or a longer distance after the onset of the attack. In his series the duration of the activity was as follows: 11 patients kept moving for 5 to 15 minutes, five for 15 minutes to one hour, four for one to two hours, and seven for 2 to 15 hours. In comparison with his results, the duration of the activity in the Finnish series (Table III) was somewhat longer. McLeod is of the opinion that this walking after the onset of acute myocardial infarct is due to the fact that the patient's "instinctive response to the pain is effort (manifested as walking) lasting from five minutes to several hours." But at least in those cases in which the physical effort was prolonged I should be inclined to think that the activity was not merely a manifestation of restlessness, but that the patient had forced himself to physical exertion regardless of the pain.

The results of the present investigation raise the question whether the unwise response to the symptoms of acute myocardial infarction—especially obvious in the men—might be a contributory factor in the mortality from this disease. It seems evident that if physical effort is obstinately prolonged in spite of the pain due to the attack the outcome may well be fatal. The following case illustrates this point.

Case 4.—In 1947 I treated a policeman aged 51 for coronary insufficiency. The man was fully aware of his condition. One day I had a telephone call to his home

and was told that he had suddenly died, a course of events common enough in this disease. However, in the dead man's home I met a friend and colleague of his, whose story of the patient's last moments was as follows. Both policemen were out on duty when my patient had a sudden attack of severe pain in the chest. He was on the point of collapsing, but, supported by his friend, he just managed to remain standing, pale and bathed in sweat. Nitroglycerin did not alleviate the pain. When his friend proposed taking a taxi to the hospital, he refused, saying: "Since we have started on foot, we shall go on foot. There is no pain in the world strong enough to make me stop." He managed to walk the distance of about 400 m. to his home and even to mount four flights of stairs to his flat on the second floor, the lift being out of order. Then, having opened the front door, he fell down dead.

It is a well-known fact that mortality from acute myocardial infarction is much higher among men than among women. In Finland the average life-span of men is, according to Kannisto (1951), 6.5 years shorter than that of women. Kannisto came to the conclusion that this difference between men and women, which is apparently greater in Finland than anywhere else, is largely due to the high mortality of middle-aged and old Finnish males from cardiac trouble. Among the causes of death acute myocardial infarction is of especial significance. The present investigation shows that there is a remarkable difference in the response of men and women to the symptoms of an attack, and to the pain of angina pectoris, and it may well be that this difference in part accounts for the high mortality from acute myocardial infarction among men in Finland.

Summary

A report is presented on the physical exertions of 102 men and 31 women immediately after the onset of acute myocardial infarction.

Only 28% of the men stopped all physical activity at once or soon after the onset of the attack. The majority (72%) continued to be active in spite of intense pain, even walking considerable distances, remaining at work, and so on. It was obvious that in many cases they had been able to keep up their efforts only by straining their will-power to the utmost. But even the severest pain did not seem to be a strong enough check to prevent them from moving.

The majority of the women (about 77%) went to rest immediately at the onset of the attack under the compulsion of the symptoms.

The response of the men was as unwise among those under 60 as among those over 60 years of age. The men who had had a previous myocardial infarction or previously diagnosed coronary insufficiency were only slightly more prudent. However, the view was taken that something might be gained by instructing patients more carefully.

It is suggested that the physical activity continued by men in spite of the symptoms of the attack may be a contributory factor in the mortality from acute myocardial infarction.

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METASTATIC ARGENTAFFINOMA SECRETING 5-HYDROXYTRYPTAMINE IN A PATIENT WITH A PATENT FORAMEN OVALE

BY

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Evidence has recently accumulated that 5-hydroxytryptamine (5-H.T.) is a specific product of the enterochromaffin cell (Barter and Pearse, 1953; Erspamer, 1954), and many of the signs and symptoms associated with carcinoid tumours seem to be directly attributable to the release of large amounts of this substance into the circulation (Page, 1958). There are, however, some facts which are not readily explicable in terms of 5-H.T. mediation. For example, the valvular and endocardial changes which are almost always associated with carcinoid with flushing attacks cannot with certainty be accounted for by 5-H.T. Some carcinoid patients exhibit a histamine-like flush which is greatly reduced by antihistamine drugs. They may also have histaminuria (Waldenström *et al.*, 1956). In others, diarrhoea, which is usually a severe symptom, is absent. It has been reported that some carcinoids contain little or no 5-H.T., and the suggestion has been made that these may constitute a group secreting 5-hydroxytryptophan (5-H.T.P.) rather than 5-H.T. (Sandler and Snow, 1958). Lastly, Lembeck (1954) has presented evidence of the presence of large amounts of a pharmacologically active substance in a carcinoid tumour in addition to 5-H.T. The studies on the present case are presented with these points in mind.

Case Report

An able seaman, aged 26, while serving in the Royal Navy in Malaya in 1951 became aware of recurrent attacks of flushing which mainly involved his face. Attacks of diarrhoea, associated with colicky pain in the right iliac fossa, began the following year and eventually became so severe that he was invalided home. Because these attacks persisted and became increasingly severe he was admitted to hospital in 1954, as a possible case of amoebic dysentery, but evidence of this infection was never found. At this time the heart was normal, and an *x*-ray examination of the chest showed no evidence of either pulmonary or cardiac disease. Because of further attacks of pain he was admitted to a hospital in Epsom in 1955, as a possible case of chronic appendicitis. Laparotomy showed that the mesentery was cicatrized, contracted, and filled with discrete softish glands, but some were hard and matted. A number of small discrete white nodules were also noted in the liver. The

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appendix, which was normal, was removed. Though the condition was regarded as neoplastic, only non-specific inflammatory changes were noted in a piece of material sent for microscopy. A subsequent barium enema showed deformity of the caecum, and at this point he was given a course of corticotrophin with marked symptomatic relief. After his discharge from hospital he remained disabled, with recurrent attacks of diarrhoea, vomiting, and abdominal pain, and was admitted in February, 1956, to the Hospital for Tropical Diseases under the care of Sir George McRobert.

On examination he was found to have a marked facial flush. The liver was enlarged and irregular, and a hard mass was palpable in the right lower abdominal quadrant. Along the lower left sternal margin a moderately loud systolic murmur could be heard, increasing on inspiration, with a thrill. A short mid-diastolic murmur, audible during inspiration, was also present. At the pulmonary area there was a faint systolic murmur, with normal splitting of the second sound. Phonocardiography confirmed these findings. Screening of the heart showed slight dilatation of the right auricle. The pulmonary artery, which was just visible, was pulsating well and appeared normal. The electrocardiogram showed no abnormality. An excess of 5-hydroxyindolacetic acid (5-H.I.A.A.) was found in the urine, and the blood level of 5-H.T. was grossly increased. A diagnosis of a metastasizing argentaffin tumour and tricuspid incompetence with stenosis was made.

Progress

The diagnosis was confirmed on February 8, when he was transferred to University College Hospital with acute intestinal obstruction. At laparotomy the terminal 4 ft. (122 cm.) of the ileum was gangrenous, the vascular occlusion being due to scarring of the mesentery and a great mass of hard matted glands in the ileocaecal angle. The gangrenous small bowel, together with the right half of the colon, was resected and normal continuity restored by an end-to-end anastomosis. A small readily accessible secondary deposit in the liver was removed for examination. Severe bronchial spasm throughout the operation caused considerable anxiety. Many flushes, affecting most of the patient's cutaneous surface, were observed during convalescence, and persistent severe diarrhoea was troublesome to the time of his discharge one month later. Microscopy of a lymph node from the operation specimen showed secondary argentaffinoma.

He had been out of hospital only a fortnight when he was again admitted with widespread oedema. Injections of mersalyl produced a profuse diuresis; treatment, initially with blood and plasma transfusion, and subsequently with a high-protein low-salt diet, controlled the oedema. After his discharge, though troubled by diarrhoea and fluid swellings of various parts of the body, he was able to do light work during the next five months. He had to be readmitted in September, 1956, because of persistent severe diarrhoea and a nutritional disturbance resembling pellagra. During the three months he was in hospital attempts were made to measure his response to treatment with 5-H.T. antagonists and possible metabolic competitors. Assessment was complicated for two reasons. He improved symptomatically on a balanced diet alone, and there was an episode of acute congestive cardiac failure during the period of observation.

The results of the investigations, which were under the direction of Professor Dent, suggested that tryptophan might be present in insufficient amounts for normal requirements. This conclusion was based on the results of urinary nitrogen determinations, which fell from about 5 g. to 3 g. a day on giving an oral supplement of tryptophan. Furthermore, the patient was found to have an almost complete inability to excrete sodium under normal conditions, although the output was greatly increased by mersalyl. His treatment on discharge consisted essentially of digoxin, mersalyl, and nicotinamide. Recurrence of his oedema, swelling of the genitalia which led to mechanical obstruction of micturition, and persistent severe diarrhoea little influenced by oral hexamethonium bromide and mist. creta cum opio, brought him back into hospital within three weeks of his discharge. Little other than symptomatic treatment could now be given. Circumcision relieved the difficulties of micturition, but severe bronchial spasm during the operation nearly led to his death. Miserable, and worn out with persistent tachycardia and severe intractable diarrhoea, he gradually deteriorated, dying in May, 1957.

Post-mortem Findings

Marked changes were found in the right side of the heart; also gross endocarditis with incompetence of the tricuspid valve and an early pulmonary stenosis with thickening and rolling of the edges of two of the valve cusps. A small patent foramen ovale was present. The edges of the mitral valve showed early thickening, and there was white capping of the papillary muscle. Pulmonary metastases were not observed, nor was the primary tumour found anywhere in the gut. The hepatic metastases had not greatly increased in size or number since operation.

Histology of Tumour Metastases.—On section the metastases were yellowish in colour. When stained with an ammonium-silver impregnation (Masson–Fontana procedure) the cells were strongly argentaffin. There was typical palisading around a central mass of grey round cells.

Biochemical and Pharmacological Observations

5-H.I.A.A. and Histamine in Urine and 5-H.T. in the Blood

The excretion of 5-H.I.A.A. in the urine was determined by the method described by Macfarlane *et al.* (1956) and the concentration of 5-H.T. in the blood by that described by Hardisty and Stacey (1955). Urinary histamine was determined by the method of Roberts and Adam (1950). The values for histamine in the urine and of 5-H.T. in the blood were obtained by Dr. R. S. Stacey and are gratefully acknowledged. The tests were performed several weeks after laparotomy.

The 5-H.T. concentration of whole venous blood was 2.2 and 2.6 μg./ml. respectively on two separate occasions. This is much higher than the normal values of 0.16 ± 0.06 μg./ml. in man (Snow *et al.*, 1955), and is of the order of the highest concentration reported in patients with carcinoid tumours (Stacey, 1957).

5-H.I.A.A. determinations were regularly done on 24-hour urine samples for a period of two weeks. The urine excretion varied from 75 to 150 mg./24 hours, a figure greatly in excess of 7 mg./24 hours found to be the mean excretion in a group of normal controls (Macfarlane *et al.*, 1956). The 24-hour histamine output in the urine was on one occasion 7.0 μg./24 hours. This amount is in the lower range of normal histamine excretion (Roberts and Adam, 1950), and is in contrast to the value of 1,100, 1,800, and 3,600 μg./24 hours reported by Macfarlane *et al.* (1956) in 3 of their 19 cases.

Analysis of Hepatic Metastases

Methods.—A liver metastasis weighing 730 mg. was obtained at operation and frozen. It was freeze-dried without thawing and then ground into a fine powder weighing 160 mg. For pharmacological testing the powder was extracted with Tyrode solution and the *p*H adjusted to 3–4 with hydrochloric acid, neutralized, and tested on the smooth-muscle preparation. For paper chromatography 12–15 mg. of freeze-dried tumour was extracted three times with 1 ml. of 95% ethanol. The extract was dried *in vacuo* and taken up in 0.25 ml. H_2O. The supernatant fluid was reduced to a small volume *in vacuo*, and placed as a narrow 1 cm. strip on Whatman No. 1 paper. A marker of 5-H.T. (10–20 μg.) was simultaneously run. Ascending chromatograms were run overnight at room temperature in *n*-butanol/acetic acid/water (Partridge, 1948) and isopropanol/hydrochloric acid (Lembeck, 1954) solvents. The

paper was examined under an ultra-violet lamp, cut into parallel horizontal strips 1 cm. wide, eluted with Tyrode solution, and tested on the isolated muscle preparation. Guinea-pig ileum or rat uterus strip was suspended in Tyrode solution at 35° C. and 26–28° C. respectively. Atropine, mepyramine, and lysergic acid diethylamide (L.S.D.) were used as antagonists in a concentration of 10^{-4} g./l. when required. Details of these methods are described by Holdstock *et al.* (1957).

Results.—Extracts of freeze-dried tumour metastases tested on the isolated guinea-pig ileum and rat uterus contained approximately 850 μg. of 5-H.T./g. of tumour. There was no significant action of smooth muscle which was not due to 5-H.T. The activity of the extract was completely abolished by L.S.D. Tests for histamine failed to reveal its presence in the tumour, the amount being less than 10 μg./g. of freeze-dried tumour. This is much less than the reported histamine content of the intestinal mucosa in man (Feldberg, 1956) and would indicate that the argentaffin cell is not a source of mucosal histamine. Eluates of paper chromatograms of tumour extract possessed pharmacological activity in an unbroken band on the paper corresponding in R_f with the 5-H.T. marker strip and indistinguishable from 5-H.T. in pharmacological properties. The same result was obtained in *n*-butanol/acetic acid and isopropanol/hydrochloric acid solvents and when the eluates were tested on either the guinea-pig ileum or rat uterus. In no instance was any pharmacological activity detected other than that satisfactorily accounted for by 5-H.T. In our experience, acid extracts of the tumour as described by Lembeck (1954) were not suitable for chromatography. With such extracts the 5-H.T. remained partly at the point of application and the remainder was found "smeared" over the paper, probably because of the high concentration of impurities.

Discussion

Our observations on this patient are in accord with the hypothesis that the severe diarrhoea and antihistamine-resistant vascular phenomena were mediated by the release of 5-H.T. into the circulation from the secondary argentaffinomata in the liver. The absence of histamine or other active substances from the tumour tissues makes it unlikely that histamine is present in the argentaffin cell or that it contributed to the diarrhoea or flushing seen in this patient. The finding of Lembeck (1954) that the liver metastases from a carcinoid tumour contained a pharmacologically active substance in addition to 5-H.T. was not found in these metastases, although various chromatographic and assay procedures were employed. Our findings in this respect are similar to those of Giarman *et al.* (1957), who examined similar metastases. It is possible that the second substance in Lembeck's experiments was an artifact of the chromatographic procedure, particularly since it was not distinguished from 5-H.T. by properties other than R_f value in the chromatography of a crude extract.

From a study of their own patient and a review of reported cases, Sandler and Snow (1958) suggested that carcinoid tumours consist of at least two histologically and "chemically" distinct types of cells—namely, argyrophil and argentaffin—secreting 5-H.T.P. and 5-H.T. respectively. The high urinary 5-H.T. excretion in the former instance would be due to the conversion of the secreted 5-H.T.P. by tryptophan decarboxylase in the kidney and the other tissues (Clark *et al.*, 1954; Gaddum and Giarman, 1956). Histaminuria and a histamine-like flush appear also to be associated with the 5-H.T.P.-secreting tumours, and Sandler and Snow suggest that significant amounts of histamine may be released from various tissues by circulating 5-H.T., which has a histamine-releasing effect on cat skin (Feldberg and Smith, 1953). In our patient, however, the flushing reaction was a mottled cyanosis, unlike that caused by histamine, and it was unaffected by antihistamine drugs. Furthermore, the tumour tissue did not contain detectable amounts of histamine.

Though our investigations cannot be extended to other possible types of carcinoid, it should be remembered that the release of histamine from skin is accompanied by pruritus and urticaria or angio-oedema in addition to erythema, in animals and in man (Paton and Schachter, 1951; Lecomte, 1956). Pruritus or urticaria has not been reported as an accompaniment of flushing in patients with carcinoid. In man, the intradermal injection of 5-H.T. fails to increase capillary permeability to circulating dye (Herxheimer and Schachter, 1959), which makes it unlikely that 5-H.T. releases histamine from human skin. The possibility that some tumours involve a cell type which secretes histamine must be considered. As yet, however, the few carcinoids examined with this in mind have not been reported to have a high histamine content.

There is as yet no satisfactory explanation for the pathogenesis of the valve lesions. The right side of the heart is the most affected, the left being relatively immune in most reported cases. Though the exact mechanism giving rise to the cardiac damage is unknown, a possible reason for this localization is suggested by Goble *et al.* (1956), who have shown in a patient with the fully developed syndrome that two-thirds of the free 5-H.T. in the blood is removed in its passage through the lungs. In the present case there was no history indicative of cardiac disease until general symptoms associated with carcinoid appeared. The patient, classified as fit for general service, had served in the Royal Navy. During an admission to hospital in 1954 his heart was found to be normal, and an *x*-ray examination of the chest showed no evidence of cardiac disease. By 1956 he had developed signs of tricuspid incompetence and stenosis. His first attack of congestive cardiac failure occurred later in the same year, eight months before he died in May, 1957. During this latter period the possibility of surgical alleviation of the severely crippled heart was considered, but because the exact cardiac lesion was unknown the idea was abandoned.

At necropsy marked changes were found in the right side of the heart. There was gross endocarditis with incompetence of the tricuspid valve and an early pulmonary stenosis with thickening and rolling of the edges of two of the valve cusps. An unusual finding was a small patent foramen ovale, which, in the absence of pulmonary metastases, probably accounted for the early thickening of the edges of the mitral valve. An identical anatomical case has recently been studied by McKusick (1956). The occurrence of mitral stenosis as well as pulmonary stenosis in the presence of a patent foramen ovale strongly supports the view that there is a humoral factor producing the lesion. It has been claimed that carcinoid tumours develop from embryonic rests, and it might be that the pulmonary stenosis is a congenital abnormality.

The gross endocarditis seen in this patient and described in others by McKusick (1956) and Thorson *et al.* (1954) does not occur in congenital stenosis. Post-mortem study of the valves indicated no similarity to specific diseases such as syphilis or rheumatic fever,

and the changes were quite different from those of congenital stenosis. It would seem, therefore, that the pathogenesis of the cardiac and valvular lesions was secondary to the release of 5-H.T. or to some other chemical substance directly or indirectly associated with the tumour tissue. Because cardiac failure appears to occur late in the disease, by which time the heart is damaged by multiple lesions—the most frequent of these being endocarditis, pulmonary stenosis, and tricuspid incompetence—cardiac surgery is likely to have only a very limited field of application in the treatment of these cases. On the other hand, extirpation of tumour tissue in an attempt to shield the heart from the baneful effects of 5-H.T. might in some circumstances be worthy of consideration.

Oedema was a most incapacitating and troublesome symptom. Not always in dependent parts, sometimes confined to the face and thighs, it occasionally became widespread. It appeared shortly after resection of the gangrenous terminal ileum. During the patient's convalescence from this operation a persistently low urinary output, in spite of adequate fluid intake and a sudden inexplicable gain of 6 lb. (2.7 kg.) in weight, preceded the onset of widespread oedema, which brought him back into hospital only 10 days after discharge. On this and subsequent occasions repeated observations of the blood pressure did not reveal any significant deviation from the normal. Mersalyl produced a profuse diuresis followed by a rapid disappearance of the oedema of the soft parts, the small bilateral pleural effusions, and the ascites. For the remaining year of his life a varying degree of oedema was associated with severe thirst and oliguria, the 24-hour urinary output persistently bordering upon 500 ml. or considerably less. It was only by weekly injections of mersalyl, the response to which was always dramatic, that he could be prevented from becoming waterlogged.

Though the antidiuretic effect of 5-H.T. has been questioned by Abrahams and Pickford (1956), it is regarded by Erspamer (1954) as a normal and important function of this substance in the body. Smith *et al.* (1957) found that the kidney was in fact able to deal with the water load in four of their cases, the study of which led them to suggest that the antidiuretic effect of 5-H.T. was inconstant because its effect upon the kidney was indirect and mediated by vascular change. Various stages of infarction of the kidneys presumably due to renal vasoconstriction have been reported in rats to which 5-H.T. was administered subcutaneously (Hedinger and Langemann, 1955; Page and Glendening, 1955). Our patient was unable to excrete sodium under any normal conditions, the 24-hour output averaging about 1 mEq. On two occasions when mersalyl was given the output immediately increased to 300 and 600 mEq, falling again to the control level within two days. Sodium retention appeared to be the immediate cause for the oliguria and persistent oedema. This would be in accordance with the observations of Hulet and Perera (1956), who have shown that the administration of 5-H.T. may be associated with significant sodium retention.

Diarrhoea, which appears to be due to increased motility consequent upon the local effect of 5-H.T. on the gastro-intestinal tract, has been little emphasized in the descriptions of the syndrome. It was this patient's principal complaint, and caused him great misery. Though it started in attacks during 1952, it was not until 1956 that it became persistent, severe, and resistant to all forms of treatment. Shortly after the onset of the severe symptoms a pellagra-like state became manifest. He became very depressed, irritable, and morose, was easily upset, and resented any interference or examination. He had a red sore tongue, and complained bitterly of severe burning pain in the rectum, great weakness, loss of muscle bulk, and cramps and pains in the legs. During this time, on giving tryptophan, there was a steady and almost certainly significant fall in the total urinary nitrogen output from about 5 to 3 g. a day, suggesting that tryptophan might have been present previously in insufficient quantities for total utilization of dietary protein.

Tryptophan, an essential amino-acid, is required not only for protein synthesis but also as a precursor of nicotinic acid. 5-H.T. is also derived from tryptophan, but in normal circumstances it is a minor metabolic pathway of tryptophan metabolism (Udenfriend, 1958). In the presence of an argentaffinoma the production of 5-H.T. is enormously increased and the major portion of the dietary tryptophan may be utilized in this way. This metabolic parasitism of the tumour was thought to be primarily responsible for the observed nutritional disturbance, which was further exacerbated by the severe diarrhoea. It is interesting to compare this situation with that occurring in Hartnup disease (Baron *et al.*, 1956), where a pellagra-like state may intervene owing to an inborn error of metabolism which causes wastage of dietary tryptophan along a rather different pathway.

Summary

A case of metastatic argentaffinoma with high urinary excretion of 5-hydroxyindolacetic acid and elevated blood 5-hydroxytryptamine excretion is described. There was no evidence of altered histamine metabolism.

The tumour metastases were found to contain high concentrations of 5-hydroxytryptamine, but no other smooth-muscle stimulant was detected.

The damage to the mitral valve as well as tricuspid and pulmonary stenosis may be explained on the basis of the patent foramen ovale found at necropsy.

Sodium retention was an unusual feature and appeared to be the immediate cause of oliguria and persistent severe oedema.

A nutritional disturbance resembling pellagra may have been due in part to diarrhoea and in part to nicotinic acid deficiency secondary to abnormal tryptophan metabolism.

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TRANSAMINASE AND LIVER-FUNCTION STUDIES IN INFECTIOUS MONONUCLEOSIS

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Clinical manifestations of hepatitis are infrequent in infectious mononucleosis, though subclinical hepatitis is believed to be common because liver-function tests are usually abnormal. However, the tests most often used to demonstrate impaired liver function, the thymol turbidity and the cephalin-cholesterol flocculation, are those which reflect alterations in serum proteins, alterations for which antibody production might be in part responsible; caution has therefore been exercised in regarding abnormal flocculation tests as evidence of liver damage. Nevertheless, Leibowitz (1953) in a review of clinical, chemical, biopsy, and post-mortem studies concluded that hepatitis was an integral feature of most, if not at all, cases of infectious mononucleosis, a conclusion confirmed by the almost invariable finding of inflammatory changes in the liver in the biopsy studies of Nelson and Darragh (1956) and Sullivan *et al.* (1957).

Wróblewski and LaDue (1956) have shown that the levels of the serum glutamic-oxaloacetic and serum glutamic-pyruvic transaminases (S.G.O.T. and S.G.P.T.) are increased in liver-cell injury, the enzymes being liberated from the damaged liver cells into the blood-stream. They also showed that determinations of these enzymes (though not actually measuring liver-cell function) more sensitively reflect liver-cell damage than do conventional liver-function tests.

Rennie and Wróblewski (1957) studied serum transaminase levels in hepatitis associated with infectious mononucleosis and concluded that most patients with infectious mononucleosis have laboratory evidence of complicating hepatitis, but in a later article Wróblewski (1958) states that infectious mononucleosis usually is accompanied by normal S.G.O.T. and S.G.P.T. activity.

A study of liver function in infectious mononucleosis using serum transaminases and conventional liver-function tests has been in progress since the beginning of 1958, and our observations and conclusions are presented below.

Materials and Methods

Twenty-three consecutive patients presenting with infectious mononucleosis during a period of 12 months were studied. These comprised 15 nurses, 1 medical student, and 3 female and 4 male patients referred by local practitioners. All but three of the patients were hospitalized, two were confined to bed at home, and one patient (Case 18) remained ambulant throughout the course of her illness.

The minimum diagnostic requirements for inclusion in the study were the presence of fever, sore throat, and lymphadenopathy, accompanied at some stage by a blood picture in which at least 50% of the total white cells were lymphocytes, and at least 10% of the total white cells were atypical lymphocytes of the type described by Downey and McKinlay (1923).

The serum heterophil antibody titre (H.A.T.) was determined in all patients and differential absorption performed, using ox red-blood-cell and guinea-pig-kidney suspension (Davidsohn, 1937). An H.A.T. of 1:28 or more, provided that absorption occurred with ox red cells but not guinea-pig kidney, was taken as a diagnostic titre (sero-positive) in this laboratory.

Sera were obtained from all patients as soon as possible after the start of illness and at intervals of three to seven days during its course: 10 patients were followed up at least three months after its onset. The start of illness was defined as the day of onset of sore throat, fever, lymph-node swelling, or gastro-intestinal symptoms.

The following chemical estimations were made: S.G.O.T. (Karmen *et al.*, 1955), S.G.P.T. (Wróblewski and LaDue, 1956), thymol turbidity and flocculation (Maclagan, 1944), colloidal gold flocculation (Maclagan, 1946), zinc sulphate turbidity (Kunkel, 1947), mercuric chloride turbidity (Maclagan *et al.*, 1957), alkaline phosphatase (King and Armstrong, 1934), total bilirubin (Malloy and Evelyn, 1937), and total protein (Van Slyke *et al.*, 1950). The normal values of these tests in the laboratory are given in Table II.

Paper electrophoresis by the hanging-strip method was also performed. 10 μl. of serum was applied to Whatman No. 3 MM filter paper saturated with barbitone buffer (*p*H 8.6, μ 0.05), subjected to a potential difference of 110 v. for 15 hours, and the strips were dried, stained with light green, and scanned, using an EEL scanner.

Clinical Findings

All patients had an illness with fever, sore throat, and lymph-node enlargement always affecting the posterior cervical and sometimes the axillary and inguinal nodes. The illness was in all cases of short duration; the average stay in hospital was 19 days, and all patients

made a complete clinical recovery. Sensitivity to alcohol for at least three months after their illness was noted by three patients (Cases 4, 5, and 6); nausea and dizziness followed the ingestion of a quantity of alcohol which prior to illness had no such effect. The illness was judged to be severe in three patients, and in two of these and in one further patient a diagnosis of accompanying hepatitis was made on clinical grounds because of the severity of gastro-intestinal symptoms. Only one patient was clinically jaundiced; four patients had a palpable liver. Antibiotics, usually penicillin, were administered to patients with severe oropharyngeal inflammation; otherwise treatment was symptomatic, and consisted of gargles, aspirin, and rest in bed until one week after fever had subsided.

Important clinical data of these cases, together with their maximal H.A.T. and haematological findings, are listed in Table I.

Chemical Findings

Table II lists the maximal laboratory findings for each patient. The serum transaminases were elevated in 18 of the 19 sero-positive cases. Sera were obtained from 12 of these within seven days of the start of the illness and raised levels were found in all. Except in one case transaminases were maximal during the second week of illness. Raised levels had usually reverted to normal by the fifth week from the start of the illness. The S.G.O.T. and S.G.P.T. values ran roughly parallel, the S.G.P.T. exceeding the S.G.O.T. in approximately two-thirds.

No correlation was observed between the transaminase activities and the H.A.T., the lymphocyte percentage, or the percentage of atypical lymphocytes in the blood. Like Rennie and Wróblewski (1957) we found that in individual patients fluctuations in clinical condition were reflected in alterations of transaminase levels, but the level of activity could not be related from patient to patient to the severity of the accompanying illness. The illness in Case 6, for instance, was much milder than that in Case 9, though the serum possessed at least double the transaminase activity.

Conventional liver-function tests were positive less often in these sero-positive cases, the thymol turbidity, for example, being raised in 12, the zinc sulphate turbidity in 14, the alkaline phosphatase in 9, and the serum bilirubin in 3. Flocculation tests were generally maximal towards the end of the second week of illness and, with the exception of the zinc sulphate turbidity, had usually returned to normal by the fifth week. They were commonly normal early in the disease, the thymol turbidity and the zinc sulphate turbidity being raised in three and six respectively of the 12 patients tested during the first week of illness. Changes in these tests could not be related to the clinical, serological, or haematological state of the patient.

Moderate elevation of the transaminases and abnormal liver-function tests were present in two of the four cases of infectious mononucleosis in which no H.A.T. could be demonstrated.

Paper electrophoresis was performed on sera taken at the height of illness from 19 of the 23 patients, and was abnormal in all, the commonest abnormality being increase of the α_2- and γ-globulins.

TABLE II.—*Maximal Chemical Data on 23 Cases of Infectious Mononucleosis*

Case No.	S.G.O.T. (Units/ml.)	S.G.P.T. (Units./ml.)	Thymol Turbidity (Units)	Thymol Flocculation	Colloidal Gold	Zinc Sulphate Turbidity (Units)	Mercuric Chloride Turbidity (Units)	Alkaline Phosphatase (Units)	Total Bilirubin (mg./100 ml.)
Normal:	5–35	5–25	0–4	0–1	0	0–4	0–4	3–13	0–1
1	130	140	8	3	4	7	9	16·0	0·8
2	167	242	4	1	3	10	—	11·5	0·1
3	428	535	5	2	2	6	6	15·5	1·6
4	38	81	8	3	5	—	5	19·0	0·6
5	32	42	5	2	1	3	5	6·5	—
6	740	600	11	4	3	10	7	14·0	0·6
7	112	65	4	0	1	4	4	10·0	0·5
8	43	22	5	2	3	6	4	6·0	0·5
9	370	184	14	4	3	12	13	64·0	2·4
10	28	9	3	0	2	4	5	5·5	0·6
11	225	175	3	0	0	5	2	10·5	0·4
12	37	33	4	0	0	7	4	7·5	0·5
13	111	148	8	2	4	12	9	12·5	0·6
14	140	162	6	0	2	8	6	11·5	0·5
15	225	310	6	2	2	6	8	24·0	1·5
16	128	163	3	0	2	3	5	9·0	0·4
17	128	132	5	0	1	5	6	35·0	0·3
18	67	62	6	2	1	2	2	6·0	0·1
19	82	126	3	1	2	5	6	14·0	0·5
20	32	10	2	0	0	2	1	8·0	0·1
21	30	18	4	0	2	7	4	8·5	0·6
22	33	45	6	0	4	8	7	9·5	0·1
23	413	180	8	3	2	5	8	14·0	0·4

TABLE I.—*Clinical and Maximal Haematological Findings on 23 Cases of Infectious Mononucleosis*

Case No.	Age	Sex	Anorexia	Nausea	Vomiting	Jaundice	Palpable Liver	Palpable Spleen	Severity of Illness	Hepatitis Diagnosed Clinically?	Treatment	Maximal H.A.T.	Maximal W.B.C. per c.mm.	Maximal % Lymphocytes	Maximal % Atypical Lymphocytes
1	18	F	Moderate	Moderate	Mild	Absent	Present	Present	Severe	Yes	Symptomatic	1 : 896	8,000	52	20
2	24	F	Absent	Mild	Absent	,,	Absent	Absent	Moderate	No	Penicillin	1 : 28	13,100	52	15
3	24	F	Mild	Absent	,,	Present	,,	,,	,,	Yes	Symptomatic	1 : 1,792	20,500	80	30
4	21	M	Moderate	Mild	Mild	Absent	,,	Present	Severe	,,	Penicillin	1 : 3,584	13,400	60	36
5	20	F	Absent	Absent	Absent	,,	,,	Absent	Mild	No	Symptomatic	1 : 112	17,400	50	12
6	20	F	,,	Mild	Mild	,,	Present	Present	Moderate	,,	Penicillin	1 : 224	10,000	86	80
7	20	F	,,	Absent	Absent	,,	Absent	,,	Mild	,,	,,	1 : 112	13,100	77	52
8	20	F	,,	,,	,,	,,	,,	,,	,,	,,	Symptomatic	Negative	9,000	51	26
9	23	F	,,	,,	Mild	,,	,,	Absent	Severe	,,	Penicillin	1 : 224	11,200	60	40
10	27	F	,,	,,	Absent	,,	,,	,,	Moderate	,,	Symptomatic	Negative	8,500	79	52
11	21	F	,,	,,	,,	,,	,,	,,	Mild	,,	,,	1 : 224	4,500	67	45
12	20	F	,,	,,	,,	,,	,,	,,	,,	,,	,,	1 : 28	8,300	68	56
13	20	F	,,	,,	,,	,,	,,	,,	,,	,,	,,	1 : 1,792	17,200	88	72
14	20	F	,,	,,	,,	,,	Present	,,	,,	,,	Penicillin	1 : 448	10,000	67	17
15	21	F	Mild	Mild	Mild	,,	,,	Present	Moderate	,,	,,	1 : 224	5,500	77	60
16	28	F	Absent	Absent	Absent	,,	Absent	Absent	,,	,,	Penicillin, tetracycline	1 : 448	10,900	67	47
17	24	M	,,	Mild	,,	,,	,,	,,	Mild	,,	Symptomatic	1 : 56	10,400	76	52
18	19	F	Moderate	Absent	,,	,,	,,	,,	,,	,,	,,	Negative	8,500	68	60
19	23	M	,,	,,	,,	,,	,,	Present	Moderate	,,	Penicillin, tetracycline	1 : 224	14,800	80	40
20	20	F	Absent	,,	,,	,,	,,	Absent	Mild	,,	Penicillin	1 : 56	11,700	54	25
21	19	M	Mild	,,	,,	,,	,,	,,	,,	,,	Symptomatic	Negative	14,000	61	52
22	19	F	,,	,,	,,	,,	,,	,,	,,	,,	,,	1 : 448	12,400	82	55
23	23	M	,,	Mild	Mild	,,	,,	Present	Moderate	,,	Penicillin	1 : 114,688	9,400	59	35

Elution of heterophil antibody was accomplished from paper electrophoretograms of the serum of four sero-positive cases, and the antibody was found to move with the γ-globulin.

Table III shows the laboratory findings on 10 patients tested at least three months after their illness. All had normal transaminases, but half had a raised zinc sulphate turbidity, minor disturbances of other flocculation tests, and increased γ-globulin on electrophoresis. The zinc sulphate turbidity chiefly measures γ-globulin; that its elevation might be related to persisting antibody was supported by the higher titres of heterophil antibody in these patients' sera.

Ten patients confined to bed with upper respiratory illness other than infectious mononucleosis, but in whom a diagnosis of infectious mononucleosis had been considered on clinical grounds, had normal transaminases and normal liver-function tests. Five cases of reticulosis (three of lymphosarcoma and two of Hodgkin's disease) which presented with fever, lymph-node enlargement, and abnormal cells in the peripheral blood had normal values for these tests.

Discussion

Increased S.G.O.T. and S.G.P.T. activity in infectious mononucleosis indicates liver involvement, for though S.G.O.T. activity may be increased in both myocardial and liver-cell injury, S.G.P.T. activity is not significantly increased in the former (Wróblewski and LaDue, 1956). The superiority of the transaminases over conventional liver-function tests in their sensitivity to liver injury and ability to reflect the patient's clinical state indicates that where transaminase determination is available other tests of liver function may be unnecessary. Like Sullivan *et al.* (1957) we found that flocculation tests gave little information about the extent or duration of liver involvement, whereas transaminase determination would seem the ideal laboratory test for following the course of illness, the effect of treatment, and the duration of liver damage. The early elevation of the transaminases was helpful in the diagnosis of cases with negative serology and an equivocal blood picture. By finding raised transaminase levels we were occasionally able to predict that the serological or haematological findings would become positive. Normal transaminase levels were found in the 10 patients with upper respiratory illness and the five with reticulosis in whom a diagnosis of infectious mononucleosis was considered but not confirmed.

Clinical (Mason and Adams, 1958), liver-function (Berk *et al.*, 1948; Sullivan *et al.*, 1957), and liver-biopsy (Nelson and Darragh, 1956; Sullivan *et al.*, 1957) studies have indicated differences between the hepatitis of infectious mononucleosis and that of infective hepatitis. The transaminase pattern also differs from that found in infective hepatitis, since the levels are lower (they exceeded 500 units per ml. in only two of our cases) and are usually maximal in the second week of illness, whereas in infective hepatitis the peak of S.G.O.T. and S.G.P.T. activity is usually in excess of 500 units per ml. and occurs in the early phase of the disease (Pryse-Davies and Wilkinson, 1958).

It has been suggested (Cohn and Lidman, 1946; Bennett *et al.*, 1950; Hsia and Gellis, 1952) that, to prevent permanent liver damage, patients with infectious mononucleosis should be treated with a regime of high-carbohydrate, high-protein, and low-fat diet, vitamin supplements, parenteral fluids if there is anorexia, and protracted rest. This treatment has been recommended because of the belief that the hepatitis of infectious mononucleosis may become chronic (Cohn and Lidman, 1946; Bennett *et al.*, 1950) or proceed to cirrhosis (Jordan and Albright, 1950; Leibowitz and Brody, 1950). The incidence of these hepatic sequelae is not accurately known, nor has the value of the proposed therapy been established. Increased serum transaminase activity in the first week of illness, and the frequency of biochemical evidence of liver damage even when symptoms and signs of liver involvement are absent, suggests that treatment considered useful in preventing liver damage should be instituted in all cases and begun as soon as the diagnosis is established. Such treatment should perhaps be continued until transaminase activities return to normal.

Our four sero-negative cases failed to reveal heterophil antibody despite repeated testing. Two of these had normal transaminase levels and two had slightly raised levels: it may be that liver injury is milder or less common in sero-negative disease.

The presence of hepatitis so frequently in the course of infectious mononucleosis suggests the possibility that the infective agent of the disease, if present in the liver, might pass from damaged liver cells via the bile into the faeces, and that ingestion of contaminated material might be responsible for some cases.

Summary

Serum glutamic-oxaloacetic transaminase (S.G.O.T.), glutamic-pyruvic transaminase (S.G.P.T.), and liver-function studies were carried out on 23 patients with infectious mononucleosis.

Raised transaminase values were observed in 18 out of 19 sero-positive cases and in two out of four sero-negative cases. The levels of activity of both enzymes

TABLE III.—*Follow-up Findings on* 10 *Cases of Infectious Mononucleosis*

Case No.	Days after Start of Illness	H.A.T.	S.G.O.T. (Units/ml.)	S.G.P.T. (Units/ml.)	Thymol Turbidity (Units)	Thymol Flocculation	Colloidal Gold	Zinc Sulphate Turbidity (Units)	Mercuric Chloride Turbidity (Units)	Alkaline Phosphatase (Units)	Total Bilirubin (mg./100 ml.)	Total Protein (g./100 ml.)	Serum Electrophoresis
4	317	1:56	27	14	4	1	1	6	3	7·0	0·1	7·4	Increased γ-globulin
5	334	1:28	9	8	2	0	1	2	1	4·5	0·6	7·1	Normal
6	95	1:56	19	8	3	1	2	6	4	3·5	0·4	7·7	Increased γ-globulin
7	181	1:28	13	9	2	0	0	1	2	6·5	0·4	6·9	Normal
8	158	Negative	13	9	2	1	1	5	3	4·5	0·1	7·5	,,
11	118	1:28	19	12	1	0	0	1	2	—	—	6·4	,,
13	102	1:224	20	15	3	1	1	6	3	8·0	0·1	7·7	Increased γ-globulin
12	144	Negative	16	8	1	0	0	3	3	3·5	0·6	6·7	Normal
15	91	1:56	20	9	2	0	0	5	3	6·5	0·1	7·5	,,
16	99	1:28	16	9	1	0	1	1	2	3·0	0·4	5·5	,,

were increased in the first week of illness, were usually maximal during the second week, and returned to normal about five weeks from its commencement. The S.G.O.T. and S.G.P.T. levels ran roughly parallel, the S.G.P.T. exceeding the S.G.O.T. in about two-thirds of the cases.

Transaminase values were below 500 units per ml. in all but two patients; high levels were not necessarily associated with severe illness. Variations in individual patients' clinical state were reflected in alterations of their transaminase levels.

Conventional liver-function tests were less often abnormal and were not affected so early. The zinc sulphate turbidity and serum γ-globulin were sometimes raised some months after recovery, when other tests were normal; this was thought to be related to persisting antibody.

Transaminase determination was helpful in early diagnosis and differential diagnosis, and may assist case management. Our findings confirm that liver involvement is a usual feature of the disease.

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GASTRO-DUODENAL HAEMORRHAGE AS A SURGICAL EMERGENCY

BY

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From this hospital, Bohn (1949) reported his experience of 150 cases of gastro-duodenal haemorrhage treated under his personal care in surgical wards. 135 were of acute or chronic peptic ulcers, 33 (25%) underwent emergency surgery, and the overall mortality was 7.4%.

Since that time changes in policy and organization have taken place, and it seemed timely to survey the situation again. The five years 1953 to 1957 are reviewed in this report. Over this period all cases of gastro-duodenal haemorrhage were admitted as routine surgical emergencies under the care of the surgeon on duty. As a result four consultant surgeons and various registrars have been responsible for the treatment of the patients, in contrast to the earlier series, in which all the cases received the individual attention of a single surgeon specially interested in the problem.

In these five years 551 patients were admitted with gastro-duodenal haemorrhage, but 11 are now excluded because the evidence concerning the haemorrhage was doubtful. Of the remaining 540 cases, 488 were due to acute or chronic ulceration; 97 of these underwent emergency surgery, and the overall mortality was 5.9%. This paper is concerned with an analysis of these statistics, and reviews some aspects of the whole period of 11 years from 1946, during which time 861 cases of haemorrhage from peptic ulcers have been treated.

Statistical Analyses

Of the 540 cases of definite haemorrhage, 488 were diagnosed as due to ulceration. The other cases were diagnosed as follows: hiatus hernia 30, oesophageal varices 10, gastric carcinoma 7, purpura 2, and ulcerated gastric polyp, leiomyoma of stomach, and haemophilia 1 each. The diagnosis of hiatus hernia needs some comment. The high incidence in this compared with earlier series is probably due to increased knowledge of the lesion, and in consequence a routine radiological search is made for it. These cases, like nearly all the others, received medical treatment, and later, when bleeding had ceased, a barium-meal examination was made. The hiatus hernia was not firmly diagnosed, therefore, until some days after bleeding had ceased. In many cases oesophagoscopy was done at this stage, but few were found to have oesophagitis. Whether this indicated that oesophagitis had settled on medical treatment, or that the hernia was a coincidental accompaniment of an acute ulcer, it is not possible to say.

The major problem in all series of this sort is, however, the haemorrhage from peptic ulceration (including both acute and chronic ulcers), and the following tables give data concerning the 488 patients in this group.

Table I shows how the group is divided according to diagnosis and sex, and gives numbers treated surgically, with the mortality rates. The "peptic ulcer" group, in which the site of the ulcer was not known, is a rather unsatisfactory one, especially so because it had a high mortality rate. In all there was a history of chronic ulceration, but the site remained in doubt

TABLE I.—*Diagnosis, Sex, Mortality, and Operative Statistics*

Diagnosis	Total	Sex		Deaths		Operations No.	%	Sex		Operation Mortality
		M	F	No.	%			M	F	
Acute ulcers	155	89	66	6	3·9	24	15·5	10	14	4
Duodenal ,,	190	142	48	10	5·3	34	17·9	29	5	7
Gastric ,,	95	59	36	5	5·3	34	35·8	23	11	2
Peptic ,,	35	29	6	8	22·8	0	0	0	0	0
Post-gastrectomy ..	13	10	3	0	0	5	38·5	4	1	0
Total ..	488	329	159	29	5·9	97	19·9	66	31	13

because the patient was either too old and frail to warrant investigation or failed to attend for radiography after discharge. In those who died, post-mortem examination was not carried out. The experience of others, and our own in previous years, is that haemorrhage from a gastric ulcer carries a higher mortality risk than that from a duodenal ulcer, but in the present series the rates are equal. It may well be, therefore, that the peptic ulcer group were in fact mostly cases of gastric ulceration.

In the post-gastrectomy group no chronic ulcers were found in the gastric remnant, the jejunum, or at the anastomosis, by radiography, gastroscopy, or at operation, and in all cases, therefore, acute ulceration must be presumed. These patients are always referred to hospital with a supposed diagnosis of anastomotic ulceration. It does not seem to be widely known that acute ulceration is quite common in the gastric remnant—perhaps even more common than in the normal stomach.

Table II shows what the possibilities are as regards diagnosis, emergency operation, and death in any individual patient, male or female, admitted with gastro-duodenal haemorrhage. The operative liability is approximately equal between the sexes, but the male mortality risk is higher than the female. This agrees with the findings in other series. Fraenkel and Truelove (1955) found the male : female mortality ratio for chronic ulcers to be 6.1% : 4.3%. Cates (1959) found a ratio for all ulcers of 6.6% : 3.2%. In this series exclusion of acute ulcer cases still leaves the males at a disadvantage, and an analysis by age does not explain the disparity.

TABLE II.—*Diagnosis, Operation Liability, Mortality, by Sexes*

Diagnosis	Males (329)			Females (159)		
	Percentage	Operative Liability	Mortality	Percentage	Operative Liability	Mortality
Duodenal ulcer ..	43·2	20·1%	9·4%	30·0	19·5%	2·7%
Acute ,, ..	27·1			35·5		
Gastric ,, ..	18·0			22·5		
Others	11·7			12·0		

TABLE III.—*Reasons for Surgery*

	No. of Ulcer Cases	Percentage of All Ulcer Cases	Percentage of Operations for Ulcer
To control severe bleeding before or within 12 hours of admission	23	4·7	23·7
Continued to bleed or bled again while on medical treatment	68	13·9	68·9
Moderate bleeding but operation within 12 hours. Much previous trouble with ulcer	6	1·2	7·4

TABLE IV.—*Age-grouping of Emergency Operation Patients*

	<29	30–	40–	50–	60–	70–	80+
Total No.	2	5	24	23	25	15	3
Percentage of age group	7·1	10·9	24·5	24·2	20·8	12·8	7·5

In Table III are given the reasons for performing emergency operations, and Table IV shows the age-grouping of the patients so operated upon. It is impossible, in retrospect, to define a "severe" bleed, which is purely a clinical decision based on the history, clinical appearance, blood-pressure, and pulse rate. Continued or recurrent bleeding is more easily defined, though not always made manifest by haematemesis or melaena. A rising or persistently high pulse rate, often associated with a fall in blood-pressure, or a persistently low haemoglobin level in spite of transfusions of several litres of blood, has been regarded as an indication of further bleeding.

Age-grouping of the surgically treated cases shows that the peak is reached in the 40–59 age range. This fits the expected pattern, since younger patients rarely bleed to death from their ulcers and consequently a more strict interpretation of the indications for surgery is applied, while the older age-groups increasingly suffer from cardiac, pulmonary, or other disorders which discourage surgery.

Types of Operation Performed

In all cases of chronic ulceration a partial gastrectomy of either a Polya or a Billroth I type was performed. Where possible the ulcer was resected, but in one patient with a very inflamed and adherent duodenal ulcer a prepyloric section gastrectomy was performed. Subsequently, bleeding continued and could not be balanced by transfusions, with a fatal result. The danger of continued bleeding if the ulcer is left *in situ*, even when the intestinal stream is diverted from it, must be weighed when considering how to deal with a difficult ulcer.

Of the cases classified as acute ulcers 14 were treated by local excision of the ulcer, 6 by partial gastrectomy, and 4 by gastrotomy and, in the absence of any specific bleeding-point, simply closure.

Four of the five post-gastrectomy cases were found to have multiple acute ulcers, and a further resection was performed. In the other case gross obesity and adhesions around the site of operation made full exploration impossible without extensive dissection, and a vagotomy was performed.

Causes of Death

In the series of 488 ulcer cases there were 30 deaths, but, following the example of other authors, one death is excluded because the haemorrhage was a minor incident in an otherwise fatal condition. This patient was already seriously ill with carcinoma of the gall-bladder with gross hepatic invasion. The haemorrhage was from acute gastric ulcers, and was not severe. The remaining 29 died from the following causes:

No Surgery.—(16 patients.) 11 bled to death (3 transfusions unable to restore blood volume; 5 too old and frail to warrant surgery; 3 unfit for surgery owing to obesity and bronchopneumonia); 3 cardiac failure—possibly anaemic in origin; 1 ulcer perforated while on medical treatment—unfit for surgery at any time; 1 died 10 minutes after admission.

After Surgery.—(13 patients.) 5 cardiac failure (2 chronic congestive failure, 3 acute failure—possibly anaemic in origin); 4 bronchopneumonia; 1 diabetes, chronic urinary infection, and obesity; 1 leaking duodenal stump; 1 continued to bleed from D.U. after prepyloric section gastrectomy.

These figures emphasize the importance of intercurrent conditions other than ulceration, resulting in the patient's death. Bronchopneumonia, cardiac

failure, and the frailty of old age appear as major factors in the cause of death in 20 out of 29 fatalities.

It is possible that the six deaths due to acute cardiac failure were avoidable. Insufficient transfusion was probably an important factor in most of them, but some may have been precipitated by over-rapid transfusion.

Table V gives the mortality rate per decade.

TABLE V.—*Mortality by Age-groups, and Proportion of Cases by Age*

	<40	40–	50–	60–	70–	80+
Deaths	0	1	3	8	11	7
Percentage of age group	0	1·0	3·2	6·7	9·4	17·5

Proportion of patients: 40 and over 86·4%; 50 and over 68·4%; 60 and over 50·9%; 70 and over 29·0%; 80 and over 7·4%.

For comparison:

Avery Jones (1957) ..	60 and over 40%;	series mortality, 7·9%	
Cates (1959)	60 ,, ,, 33%;	,, ,,	5·4%
Ogilvie *et al.* (1952)	60 ,, ,, 30%;	,, ,,	5·3%
Fraenkel and Truelove (1955)	50 ,, ,, 65·8%;	,, ,,	5·6%.

Discussion

Comparative Statistics.—As has been pointed out repeatedly in previous papers, the fact that the mortality rate rises steeply with advancing years makes exact comparison between one series and another unrealistic. The best that can be achieved is to state the proportions in the series of patients over certain specified ages, giving due allowance for this in making comparisons. In Table V these proportions are stated and compared with four recently published series. Another factor, even less easy to compare, is the severity of the haemorrhages. It is a policy in this hospital never to refuse admission to a surgical emergency; therefore it is possible that this series contains a higher proportion of minor haemorrhages than would be included by a hospital in an area where practitioners have difficulty in finding beds for their emergencies.

Selection of Patients for Surgery

The rational course to follow in treating gastro-intestinal haemorrhage is undoubtedly to select for operative treatment any patient who is judged to be in real danger of bleeding to death, and to treat all the rest medically. In recent years all published papers have followed this course, but have shown considerable variation in the proportion so selected for operation.

The basis for selection in this series was the same as that applied by Bohn (1949) in the first series reported from this hospital. Briefly, surgery may be indicated: (1) if the haemorrhage is unduly severe (indicating involvement of a major vessel: (2) if bleeding continues or recurs while on medical treatment; (3) if the patient is over 40 years of age; and (4) if the patient gives good evidence of having chronic ulceration.

Clearly these criteria are only indications, and leave wide scope for variation in interpretation and emphasis. In Bohn's series (from 1946 to 1948) 25% were operated on with a series mortality of 7.4%. In the next two years, during which the criteria were interpreted with more emphasis towards surgery in an attempt to improve on these figures, the emergency operation rate was increased to 54%, but the mortality rose to 8.3%. While these figures are not strictly comparable (35% of patients over 60 in the first series and 45% in the second), it is clear that the increased operation rate did not improve the results. In the present series the operation rate has fallen to 20%.

This figure of 20% is still higher than that for other series. The following are corresponding figures from four recent papers: Avery Jones (1957) 10%, Ogilvie *et al.* (1952) 10%, Cates (1959) 13.5%, Fraenkel and Truelove (1955) 16.4%. In comparing these figures it is important to take into account the age factor. The average age of our patients, and those of Fraenkel and Truelove, seem to have been higher than those of all other series, so that more of our patients would fall into the group in which surgery is indicated.

Selection of the correct time for surgery may also vary considerably. In this paper "immediate surgery" has been classified as within 12 hours of admission, a time chosen to indicate that medical measures had played no real part in treatment. In the 1946–8 series 50% were immediate operations, while in the present series only 24% were so treated, without increasing the mortality rate. It is possible that in the immediate post-war years a higher proportion of really severe bleeding occurred, but it seems likely that the greater part of this fall is due to an increased tendency to wait and see if the bleeding recurs. It suggests that, provided blood transfusion is given to maintain the patient in a fit state for surgery at any moment, this initial wait-and-see policy is not unduly risky. It must, however, be stressed that in cases with a very severe haemorrhage, or with continued or recurrent haemorrhage, a wait-and-see policy might well prove disastrous.

Surgical Treatment of Acute Ulcers

It seems to be a widely accepted practice to perform a gastrectomy in all cases when palpation of the stomach fails to reveal a chronic ulcer or other definite cause for the haemorrhage. Ogilvie *et al.* (1952) state that they do not favour gastrotomy, because an acute ulcer is seldom found.

The experience in this hospital is at variance with this view. Since 1946, in 42 cases in which a gastrotomy has been performed because no chronic ulcer was palpable, a definite acute ulcer was found in 23, leaving the surgeon in no doubt about the cause of the bleeding. In these 23 patients the ulcer was excised down to the muscle coat, the bleeding vessel underrun, and the mucosa sewn over the defect. In no case did further bleeding occur.

It is argued that acute ulcers do not require surgery unless they bleed, and therefore the essential point of surgery is to stop the bleeding. Gastrectomy may be necessary to achieve this, but often it is not. To perform a gastrectomy when a lesser procedure will suffice to stop bleeding would seem quite illogical. Not only is a major operation being performed to remove a lesion which would in almost all cases heal spontaneously, but it does not prevent subsequent acute ulceration.

In none of our locally excised ulcers has chronic ulceration developed later at the site of excision. Possibly in a larger series of cases a few such chronic ulcers would develop, but this seems a weak argument for advising gastrectomy in all cases.

The situation is much more difficult when gastrotomy fails to reveal an ulcer with a definite bleeding-point, especially when the stomach and proximal jejunum are empty of blood. If the indications for surgery were unequivocal, then a gastrectomy is almost certainly justified, but, if not, it may be wisest to admit that an error has been made and close the abdomen.

General Improvement in Results

Since the war there has been a steady improvement in the reported results of treatment. In some series the mortality rate has fallen dramatically (Oxford 19% in

1949, 5.3% in 1955), while in others a low mortality rate has been maintained in spite of an increasing proportion of elderly patients (Avery Jones, 7.9% mortality rate maintained, with an increase from 33% over 60 in the earlier years to 40% later). The figures for the 11 years in this hospital are:

1946–48	..	7·4% mortality	..	35% over 60
1949–51	..	8·3% ,,	..	45% ,,
1951–53	..	7·0% ,,	..	49% ,,
1953–57	..	5·9% ,,	..	51% ,,

There is probably no single explanation for the general improvement. An expanded range of antibiotics and anaesthetics agents has undoubtedly helped, but probably increased understanding of the problem, crystallized by Avery Jones in 1947, has played the most important part.

Summary

Of 541 cases admitted suffering from gastro-duodenal haemorrhage 488 were due to acute or chronic peptic ulceration. Of these 488 cases, 97 were treated by emergency operation. The overall mortality was 5.9%.

The frequency and timing of emergency surgery are discussed. A frequency of 20% was found in this series. Comparing this with previous series from this hospital, it does not appear that the mortality rate will be reduced by resorting to surgery more often than this. The number of " immediate " operations (within 12 hours of admission) has tended to fall in this hospital, but nevertheless the dangers of delay in severe or repeated haemorrhage are stressed.

It is suggested that acute ulceration often occurs in the post-gastrectomy stomach. In this series probably all the post-gastrectomy haemorrhages were from acute rather than chronic recurrent ulceration.

It is argued that gastrectomy for haemorrhage from acute ulcers is often illogical and unnecessary.

I thank Mr. F. H. Aitken Walker, Mr. G. Bohn, Mr. R. G. Reid, and Mr. C. Latto for permission to study the records of their patients and to publish this paper. I am particularly grateful to Mr. G. Bohn whose precepts regarding gastro-duodenal haemorrhage I have attempted to follow. I also thank the records department of this hospital, who sorted out over 2,000 case-histories for my perusal.

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Medical Memoranda

"Contrecoup" Fracture of the Sternum

Fractures of the sternum are rare. Holderman (1928) found 62 cases among 46,237 fractures of all types; an incidence of 0.13%. They are usually caused by direct violence. Fractures of the sternum produced by indirect violence are exceedingly uncommon. They have been produced by muscular action in lifting, coughing, labour, and tetanus. "Contrecoup fractures of the sternum," so called by Tarnowsky (1905), are caused either by falls on the head and shoulders, or by the fall of a heavy object on the back of the cervico-dorsal spine, so that the thorax and neck are brought into forcible anteflexion. The fracture thus sustained in the adult is at or near the junction of the manubrium and gladiolus, the latter overriding the former. Tarnowsky, who added 7 cases to 20 previously described by Servier (1889), summarized the mechanism producing these fractures as follows.

(1) Falls on the head and shoulders press the ribs forward and upward, the range of motion increasing from the first to the seventh pair. (2) The clavicles may sometimes act as a lever and help to wrench the manubrium from the gladiolus. (3) Intrathoracic pressure at the time of the fall exerts a positive pressure on the thoracic wall. (4) The second costal cartilages act as a wedge tending to separate the manubrium from the gladiolus.

Gurlt (1864), Brunn (1913), and Kirkham (1941) reported fractures of the sternum sustained in a similar manner. Many of the fractures were caused by violent injuries producing associated fractures of the cervico-thoracic vertebrae and ribs.

No associated bony injury was present in the following case. The fracture was produced indirectly by the patient falling on his back, the cervico-dorsal spine being acutely anteflexed.

CASE REPORT

A man aged 43 slipped while descending some stairs and fell backwards. He slid down about 16 stairs on his back, feet foremost. His cervico-dorsal spine was acutely anteflexed partly as a result of the fall and partly voluntarily, to avoid hitting the back of his head on the stairs during the descent.

On admission to hospital on December 21, 1958, he complained of severe pain over the front of the sternum which came on immediately after the fall. He was pale; pulse 76, B.P. 150/100. His breathing was mainly abdominal, and he was holding his head in one position to prevent pulling on the sternum through the sternomastoid. He was a well-built man. Localized tenderness and slight swelling were present over the sternum, just below the sterno-manubrial joint. No obvious deformity of the sternum was seen. There was bruising over the right buttock and left scapula. No abnormality was found in the heart and lungs. *X*-ray examination revealed a fracture of the sternum 2 cm. below the sterno-manubrial joint, with anterior displacement of the lower fragment. No abnormality was seen in the ribs, dorsal vertebrae, or intrathoracic organs.

He was treated by bed rest and analgesics. No attempt was made to reduce the displacement. Ten days after the accident he was discharged from hospital, and began work five weeks later. *X*-ray examination six weeks after the injury showed the position of the fracture to be unchanged. Bony union was occurring.

I thank Mr. G. O. Jelly for permission to publish this case.

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The World Health Organization has announced that in 1959 only 72,000 cases of smallpox were reported throughout the world as against 242,000 cases in 1958. These statistics, which do not include mainland China, show that the incidence of smallpox was much lower in India and East Pakistan. (United Nations Information Centre.)

Reviews

B.M.A. DISSECTED

Pressure Group Politics. The Case of the British Medical Association. By Harry Eckstein. (Pp. 168. 16s.) London: George Allen and Unwin, Ltd. 1960.

It is often salutary, if sometimes disturbing, to see ourselves as others see us. Sponsored by a Social Science Research Council, Dr. Eckstein, from the Center for Advanced Study in the Behavioral Sciences of Stanford, California, has passed some time in England examining the National Health Service, which attracts the same anxious attention in medical and sociological circles across the Atlantic as the progress of Russian nuclear physics does in the mind of the average American citizen. The title of his book implies that the B.M.A. is a political pressure group, and it is therefore important to know what is meant by the term. Unfortunately there is no agreement. In the preface the conflicting views of various authorities are set out, and, after reviewing them, Dr. Eckstein sums up :

> "We include under this label all groups which collectively pursue common political goals (excluding . . . parties, i.e. groups that seek directly to govern); that these groups may be, and almost always are, engaged in activities other than political activities; that the goals they pursue may be interests or 'causes,' and the means they use sanctions, arguments or petitions. Anyhow, that is how I mean the term."

The definition is wide enough to include practically every form of organized social activity and in that sense is unobjectionable.

From the chapter on "Theoretical Framework; the Determinants of Pressure Group Politics" no clear impression of any coherent theory emerges from the discussion of the relevant facts, but the author does well to emphasize the effects of recent changes in English political practice. The most important of these has been the tendency in Parliament to confer on ministers the right to make laws by regulation—a process described by Lord Hewart some years ago as "The New Despotism." An inevitable result has been the concentration of great power in administrative departments of the Government, and it is not surprising therefore that the chief political work of the B.M.A. during recent years has been patient and detailed negotiation with officials of the Ministry of Health on a "staggeringly wide range of subjects." Dr. Eckstein, indeed, comes to the conclusion that for most of the time the Association has collaborated successfully with the Ministry in a sort of "non-statutory partnership," and has supplied technical information and advice without which the Health Service would have collapsed in confusion. Personal experience during the past two and a half years convinces me that the statement is true, and the people of this country may well be grateful that there are sufficient public-spirited doctors who are willing to sacrifice their leisure to this tedious and unrewarded work.

The assertions that there has been a complete change in the character of the B.M.A., that it began as an "organization for sponsoring scientific activities and fellowship among doctors" and that it is now "a public relations office, a trade union . . . and a collective bargaining agent with the government" seem to me exaggerated and unjustified. We must admit that controversy about conditions of service has absorbed undue attention and public notice : controversy, after all, is news and agreement after negotiation is not. The evidence that Dr. Eckstein brings forward in support of these statements is the increased size of the *Supplement* of the *B.M.J.*, which records political activity, comment in the daily press, and also the sanctions implied by the formation of the Medical Guild and by the threatened withdrawal. In any event the greater size of the *Supplement* is negligible when compared with the vast increase of the scientific publications of the Association —not only the *British Medical Journal,* but the special journals, which at times have involved considerable financial loss. Clearly there has been no neglect by the Journal Committee of the duty to sponsor and aid scientific activity. There is no mention of the important work of the Overseas Committee on behalf of the medical services in the Commonwealth and Colonies, of the Library Committee, or of a number of others. Presumably they were ignored because they have no political aim and even less trade-union content, yet any description of the B.M.A. which omits them must be ill-balanced and misleading. The Medical Guild with its defence fund and the threat of withdrawal admittedly savour of trade-union practice. For me they are a necessary nuisance—like the deterrent hydrogen bomb to be used only in the last extremity. It should be remembered, too, that the B.M.A. has no disciplinary sanctions; it can neither picket surgeries nor impose penalties on members who act contrary to official policy.

Dr. Eckstein has some interesting comments on the structure and effectiveness of the B.M.A. He asserts that it does not now recruit to its service as many men of high professional distinction as does the American Medical Association. High professional distinction is rarely compatible with long hours of dreary negotiation, and if something could be done by administrative reform (perhaps by an increase in the secretariat and an extension of their power and responsibility in reaching decisions) to lighten the burden of those who accept office more distinguished men might be attracted to the work.

In appearance the Association by its large membership is "monolithic"; in fact, because many of its members have loyalties to other corporate bodies—such as the Royal Colleges—unanimous support of official policy is never certain, and this Dr. Eckstein finds diminishes its effectiveness in conflict as the monolith crumbles. Conflict, on the other hand, is not the aim of a professional association, and it may not be altogether a bad thing that belligerent policy should be subject to internal checks of this kind. In discussing public "attitudes" to the work of the B.M.A. it is strange that Dr. Eckstein did not discover its greatest asset. Whatever the public thinks or the press reports of the political work of the Association, there is happily little doubt that the English people still retain an affectionate respect for the great majority of its individual members as doctors and as friends.

A. P. THOMSON.

PORTAL HYPERTENSION

The Pathology and Management of Portal Hypertension. By R. Milnes Walker, M.S., F.R.C.S. (Pp. 113+vii; illustrated. 35s.) London: Edward Arnold (Publishers) Ltd. 1959.

The last 15 years have seen a resurgence of interest in the portal system in man, an area hitherto relatively exempt from both scientific investigation and surgical attack. This can be attributed to the development of methods for measuring the portal pressure and the use

of trans-splenic portal venography for demonstrating the ramifications of the portal venous system radiologically. Improvements in anaesthesia and the techniques of vascular surgery now allow the portal vein to be operated upon with safety.

Professor Milnes Walker and his team at Bristol have been in the forefront in both the investigation and the surgical treatment of portal hypertension. This monograph is based on their experiences in treating their first 200 cases. After brief accounts of the anatomy and physiology of the portal system, the causes and effects of portal hypertension are described. Then follow the clinical aspects and the management of the individual case. The sections on the surgical treatment are, as one might expect, outstanding, the photographs and diagrams adding greatly to the descriptions of the various procedures. Professor Milnes Walker rightly emphasizes the value of portacaval anastomosis for the carefully selected patient with cirrhosis complicated by bleeding oesophageal varices and who has good liver function. His results, too, are quite remarkable, only four of 85 patients dying in the immediate post-operative period and only four suffering further haemorrhage. Little mention is made of the problem of the patient with bleeding varix who has insufficient hepatic reserve to allow portacaval anastomosis. Perhaps the treatment in this case is the unfortunate lot of the physician. The reader should, however, be made to realize that not all patients with cirrhosis and bleeding varix are candidates for, and will benefit from, this procedure. A minor criticism is of the statement on page 62 that in the emergency treatment of haemorrhage "rest in bed, sedative drugs, and blood transfusion are the initial lines of therapy." This should be modified in a later edition, for injudicious sedation in such patients frequently precipitates hepatic coma.

This book is compact and is well written and produced. It can be confidently recommended to post-graduate students preparing for higher examinations in medicine or surgery, and for the general reader anxious to keep abreast of a rapidly developing field of medicine.

SHEILA SHERLOCK.

CHOLESTEROL

Cholesterol. By David Kritchevsky. (Pp. 291+ix; illustrated. 78s.) New York: John Wiley and Sons, Inc. London: Chapman and Hall. 1958.

The wide distribution of cholesterol in living tissues and its rather special physico-chemical properties have long intrigued all manner of biologists. Forty years ago the chemistry of this complex substance became the privileged hunting ground of those who could wield the esoteric weapons of chemical structural analysis. Recently the biosynthesis of cholesterol and other sterols has been a fruitful study for many biochemists. The possible role of cholesterol in atherosclerosis has now pointed to this substance as being possibly of very great medical importance, quite apart from the fact that it might be implicated in tumour production. It is therefore to be expected that a book should appear dealing with the biological function and significance, the chemistry, biochemistry, and physiology of this important substance. The titles of the seven chapters outline the main themes of the work: chemistry of cholesterol; biosynthesis of cholesterol; absorption and transport of cholesterol: metabolism of cholesterol; cholesterol in disease states; the blood cholesterol; and analysis of cholesterol. In addition an appendix gives data about cholesterol itself, and the amounts in which it is present in food, tissues and tissue fluids, and milk. Each chapter is well documented, and the book as a whole provides a conveniently concentrated account of what is undoubtedly a substance of great biological importance in both health and disease.

F. G. YOUNG.

PERIPHERAL VASCULAR DISEASE

Peripheral Vascular Diseases. An Objective Approach. By Travis Winsor, M.D., F.A.C.P. Foreword by Burrell O. Raulston, M.D. (Pp. 845+xviii; illustrated. £6 5s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

This monograph is intended for the student, the physician, and those concerned with the circulation. Inevitably an almost impossible task is unfulfilled. The book centres round some 400 simple diagrams with lettering so large that the visual acuity of American physicians becomes suspect.

The author is a well-known worker on the circulation with plethysmographic techniques, and some will find the method of presentation useful and easy to grasp. Other workers in this field, however, are likely to be disappointed and discover many points for criticism. One of the most serious is that the author appears not to have measured intravascular pressures directly, and to have depended on cuff methods for the usual calculation of vascular resistance from the supply pressure and the flow. Thus, on page 209, a table purports to give systolic pressures for different parts of a limb. The figures are untrue for intra-arterial pressure measured directly, and show only the well-known deviations produced by cuff artifact. For the same reason the author is in no position to discuss haemodynamics distal to an arterial block. Provided these defects are appreciated or ignored, the clinical section might prove useful to the busy general physician or the candidate for a higher qualification with no time to waste on thought.

E. P. SHARPEY-SCHAFER.

OVER-RATING THE RECENT

Contributions to Modern Psychology. Selected Readings in General Psychology. By Don E. Dulany, jun., Russell L. DeValois, David C. Beardslee, and Marian R. Winterbottom. (Pp. 398+x. 26s.) New York and London: Oxford University Press. 1958.

This volume contains reprints (some abridged) of 42 papers from the psychological literature—mostly American and over half published in the last decade. They have been chosen, so the editors tell us, "for their relevance to basic concepts of introductory psychology as well as for their readability and immediate interest value." In fact, this is a very mixed bag. A few papers are concerned with basic issues, quite a few are readable, and one or two might conceivably be said to possess "immediate interest value" (whatever that may mean). The authors represented extend from Sir James Frazer and Sigmund Freud to B. F. Skinner and D. O. Hebb. Although this selection is not at all badly done, it is doubtful whether any particular educational value can be claimed for it. Among papers of some interest to medical readers may be mentioned the original report by Benton, Heron, and

Scott on the "perceptual isolation" work carried out some years ago at McGill University, a summary by Olds of recent work on intracerebral self-stimulation in rats and monkeys; and a reprint of Mowrer's early paper on anxiety and learning, which did much to bring psycho-analytical concepts within the purview of behaviour theory.

This volume gives evidence of the high degree of experimental talent and theoretical acumen in current American psychology. But it reveals also the tiresome tendency to over-rate the recent and to suppose that practically everything which psychologists do must perforce be represented irrespective of intellectual merit.

O. L. ZANGWILL.

SCIENCE AND RELIGION

Science, Medicine, and Morals. A Survey and a Suggestion. By Charles E. Raven, D.D., D.Sc., F.B.A. (Pp. 189. 15s.) London: Hodder and Stoughton. 1959.

This book represents an expanded version of a course of lectures delivered in 1958 at the College of Medicine of the University of Cincinnati. In it Dr. Raven, scientist, philosopher, and theologian, brings learning, wisdom, and experience to the study of religion and science. In four chapters sketching the medical contribution to scientific development he shows that from the days of the great Greeks—Alcmaeon of Croton, Anaximenes, Empedocles, and Hippocrates—medical thinkers have believed in the unity of soul and body. Historically, Jewish and Christian monotheism has helped scientific inquiry and the sense of moral responsibility. The idea of revelation does not exclude progress, for it represents a communication between the Divine and the human. With this comprehension the doubts and scepticism which beset the scientists of the nineteenth century in their emancipation from the traditional dogmas of Theism disappear. The Bible is pre-scientific, but spiritual faith has encouraged and nurtured experimental science. In an ordered universe knowledge awaits the investigator and one discovery leads on to another. A veil will always remain, for, as Buddha, Socrates, and Kant all taught, there are limits to our knowledge, and Max Müller termed philosophy the knowledge of these limits.

In discussing the problems of pain and evil Dr. Raven considers that the struggle to overcome pain is part of the struggle to overcome evil. Finally he suggests that mass-hysteria, which plays such havoc with men and nations, should be capable of medical analysis, if not treatment. "We shall never get a really happy people until we have a much more carefully considered and healthfully motivated public life." In this suggestion and in all the chapters of this book there is much food for thought.

ARTHUR S. MACNALTY.

The National Institutes of Health Russian Scientific Translation Program, U.S.A., has issued *A Directory of Medical and Biological Research Institutes of the U.S.S.R., 1958* (P.H.S. Publication No. 587), which is available on request. It serves not only as an address list for facilitating the exchange of scientific information, but as a useful general guide to the hierarchy of medical and biological research in the U.S.S.R. (Department of Health, Education, and Welfare, Bethesda, 14, M.D., U.S.A.; 340+vi pp.; free on request; name and subject index.)

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Health Physics in Nuclear Installations. Symposium organized at the Danish Atomic Energy Centre of Risö, May 25-28, 1959, by O.E.E.C. and the Danish Atomic Energy Commission. (Pp. 410: illustrated. 37s. 6d.) Paris: O.E.E.C. and European Nuclear Energy Agency. London: H.M. Stationery Office. 1959.

Allergie und Allergische Erkrankungen. Volume II. Edited by D. Rajka, with 21 contributors. (Pp. 1,003; illustrated.) Budapest: Akadamiai Kiado. 1959.

American Handbook of Psychiatry. In two volumes. Editor: Silvano Arieti. Editorial Board: Kenneth E. Appel, Daniel Blain, Norman Cameron, Kurt Goldstein, and Lawrence C. Kolb. (Pp. Vol. I: 999+xix; Vol. II: 1,000-2,098+ix; illustrated. £10 10s.) New York: Basic Books, Inc. London: Mayflower Publishing Co., Ltd. 1959.

Pyelonephritis. By Fletcher H. Colby, M.D. (Pp. 214+vii; illustrated. 60s.) Baltimore: Williams and Wilkins Company. London: Baillière, Tindall and Cox, Ltd. 1959.

Ciba Foundation Symposium, Jointly with the International Union of Biological Sciences, on Biochemistry of Human Genetics. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P., and Cecilia M. O'Connor, B.Sc. (Pp. 347+xii; illustrated. 50s.) London: J. and A. Churchill, Ltd. 1959.

Ciba Foundation Tenth Anniversary Symposium on Significant Trends in Medical Research. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P., Cecilia M. O'Connor, B.Sc., and Maeve O'Connor, B.A. (Pp. 356+xii; illustrated. 50s.) London: J. and A. Churchill, Ltd. 1959.

Ciba Foundation Colloquia on Ageing. Volume 5. ***The Lifespan of Animals.*** Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P., and Maeve O'Connor, B.A. With cumulative index to Volumes 1-5. (Pp. 324+xii; illustrated. 48s.) London: J. and A. Churchill, Ltd. 1959.

Biological Organisation: Cellular and Sub-Cellular. Proceedings of a Symposium organised on behalf of U.N.E.S.C.O. By C. H. Waddington. (Pp. 328+xviii; illustrated. 70s.) London, New York, Paris, Los Angeles: Symposium Publications Division, Pergamon Press. 1959.

Anatomy: Regional and Applied. By R. J. Last, M.B., B.S. (Adel.), F.R.C.S. Second edition. (Pp. 741+xvi; illustrated. 80s.) London: J. and A. Churchill, Ltd. 1959.

Cancer of the Cervix: Diagnosis of Early Forms. In Honour of Dr. C. Kaufman. Ciba Foundation Study Group No. 3. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P., and Maeve O'Connor, B.A. (Pp. 114+viii; illustrated. 12s. 6d.) London: J. and A. Churchill, Ltd. 1959.

Antithrombotic Therapy. By Paul W. Boyles, M.D. (Pp. 131+vii; illustrated. $5.) New York and London: Grune and Stratton. 1959.

Clinical Toxicology. By C. J. Polson, M.D. (Birm.), F.R.C.P., M.R.C.S., and R. N. Tattersall, O.B.E., M.D. (Lond.), F.R.C.P. (Pp. 589+xi. 42s.) London: English Universities Press, Ltd. 1959.

Natural Selection in Human Populations. Symposia of the Society for the Study of Human Biology. Volume II. Edited by D. F. Roberts and G. A. Harrison. (Pp. 76+viii. 20s.) New York, London, Oxford, Paris: Symposium Publications Division, Pergamon Press. 1959.

Der Liquor Cerebrospinalis im Kindesalter. By Professor Dr. H. Schönenberg. (Pp. 190+viii; illustrated. DM 29.) Stuttgart: Georg Thieme Verlag. 1960.

Oxosteroids. The Use of Phenolic Hydrazides for Detection, Characterisation, and Estimation. By Bernard Camber, M.D. (Pp. 79+viii; illustrated. 12s. 6d.) London: H. K. Lewis and Co., Ltd. 1960.

The Pharmaceutical Society of Great Britain. Calendar 1959-1960. (Pp. 306. 20s.) London: Pharmaceutical Press. 1959.

Biochemical Values in Clinical Medicine. The Results following Pathological or Physiological Change. By Robert Duncan Eastham, B.A. (Cantab.), M.D. (Cantab.), D.C.P., Dipl. Path. (Pp. 148. 15s.) Bristol: John Wright and Sons, Ltd. 1960.

An Introduction to Genetics. By C. M. M. Begg, M.A., B.Sc., Ph.D. (Pp. 292+xi; illustrated. 35s.) London: English Universities Press, Ltd. 1959.

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MANAGEMENT OF THROMBOCYTOPENIC PURPURA

Primary thrombocytopenic purpura is seen quite often in medical clinics. The patients are children, adolescents, and young adults; the condition is rare over the age of 45. The patient has a rash of small petechiae or large painless ecchymoses, or both. Bleeding from mucous membranes, especially from nose and gums, is frequent; sometimes menorrhagia is the presenting sign. The blood count shows platelets diminished below 40,000 per c.mm., as compared with the normal 250,000 per c.mm., and the bleeding time is correspondingly prolonged. It is of the utmost importance to establish whether this is a primary purpura, or whether it is due to taking toxic drugs or is secondary to another blood disease.

In acute leukaemia and in aplastic anaemia the first sign is sometimes a thrombocytopenic purpura. The distinction is most effectively made by examining the sternal marrow, which in primary thrombocytopenic purpura should show an active normoblastic response to loss of blood, and megakaryocytes should be present; some of the megakaryocytes may be primitive or abnormal forms, but it is not necessary to find these to establish the diagnosis. Apart from possible abnormal megakaryocytes, there should be no abnormal cells present in the bone-marrow smears. In acute leukaemia many primitive leucocytes will be present, and in aplastic anaemia all cell types are grossly diminished.

Two clinical types of primary thrombocytopenic purpura are recognized: (1) the acute type, in which the rash with bleeding from mucous membranes comes on in a few days and causes serious loss of blood; (2) the chronic type, in which recurrent crops of purpuric spots occur over some weeks and bleeding from mucous membranes is rarely severe; menorrhagia may be troublesome. These two clinical types require different management. The acute type is commoner in children and young women; spontaneous remission is fairly frequent and response to steroid treatment often good. In the chronic type spontaneous remission is rare and response to steroids often poor; splenectomy is needed in most cases. In the past two years the results of three surveys of the effects of treatment in thrombocytopenic purpura have been published, and between them they point the way to a more rational method of treating the disease.

W. Dameshek and co-workers[1] gave prednisone in 11 acute and 19 chronic cases of thrombocytopenic purpura. The maximum doses varied from as little as 20 mg. to as much as 250 mg. daily. Ten out of the 11 patients with the acute disease responded with a rise in platelet count; 12 out of the 19 with chronic disease also showed a rise. But in many patients the effect did not last once the prednisone was stopped or was reduced to 5–10 mg. daily; within 10–30 days the platelet count was again low. A sustained remission occurred only in three acute and three chronic cases, and these patients did not require any further treatment.

E. J. Watson-Williams, A. I. S. Macpherson, and Sir Stanley Davidson[2] at Edinburgh studied a large group of 93 patients. They divided their patients into those with a short history of less than 100 days and those with a long history of more than 100 days. No specific treatment, for some reason or other, had been given to 26 patients, 16 with short and 10 with long histories. In the group of 16 short-history patients, 12 had recovered spontaneously and 4 had died from cerebral haemorrhage; only one remission occurred among the 10 long-history patients, and 3 of them had died, one from gastro-intestinal haemorrhage and 2 from causes unrelated to the purpura. A second larger group had been given steroid therapy —cortisone, prednisone, or A.C.T.H. Nineteen of these were short-history cases, and among them 9 had persisting remissions, 1 a temporary remission, and in 9 there was no response. Seventeen long-history cases were treated before splenectomy, and 8 of these had a remission, but the remission was never maintained for more than 60 days. Splenectomy was performed in 33 long-history patients, and in 14 of these steroids were given as well; 12 months after the operation 29 patients were seen and 19 were free from symptoms. The Edinburgh workers conclude that in patients with a history of less than 100 days spontaneous remission is quite likely and can be hastened by steroid treatment; this treatment should therefore be given a trial in such patients. When steroid treatment failed, then splenectomy was found to be

[1] Dameshek, W., Rubio, F., Jr., Mahoney, J. P., Reeves, W. H., and Burgin, L. A., *J. Amer. med. Ass.*, 1958, **166**, 1805.
[2] Watson-Williams, E. J., Macpherson, A. I. S., and Davidson, S., *Lancet*, 1958, **2**, 221.
[3] Carpenter, A. F., Wintrobe, M. M., Fuller, E. A., Haut, A., and Cartwright, G. E., *J. Amer. med. Ass.*, 1959, **171**, 1911.

successful in 75% of the cases. In patients with a history of more than 100 days, spontaneous or steroid-induced remission is unusual or not sustained; splenectomy is usually needed, but was successful in only 50–60% of the Edinburgh patients.

Results with another large group of 85 patients have recently been published from M. M. Wintrobe's department at Salt Lake City by A. F. Carpenter and co-workers.[3] They were particularly careful to ensure that their cases were really primary thrombocytopenic purpura. They excluded of course all patients who had another blood disease or who had had drugs apt to cause thrombocytopenia. They looked especially for systemic lupus erythematosus and watched all their patients for the later appearance of this disease, but, in fact, it occurred only once, 12 months after splenectomy for a thrombocytopenic purpura that had been present for three years, and suggestive signs were present before the operation. Finally they excluded any cases if the histology of a removed spleen showed abnormalities not usually associated with thrombocytopenic purpura. They divided their patients into 4 groups according to the way they were managed. The first group of 24 patients received no steroids and did not have splenectomy; 10 of these patients, all children under 10 years old, had a complete spontaneous remission; 2 died of cerebral haemorrhage. The second group of 16 patients received steroids; 10 of these had a complete remission, 8 of them being children under 10 years old. The third group had their spleens removed and were not given any steroids; there were 26 of these patients and complete remissions lasting more than 12 months were obtained in 17; in 3 the remission was satisfactory but had not lasted 12 months at the time of writing, in 3 others the remission was only partial, and in the remaining 3 there was no improvement at all. Finally 19 patients had both steroid treatment and splenectomy; satisfactory remission occurred in 8 for over 12 months and in 4 more who had not completed the 12 months after operation; 2 showed partial remission, 3 had no remission, and in 2 the result was doubtful.

Like the Edinburgh workers, they note that the duration of the purpura is important in assessing likely results. For example, no spontaneous remission, and only one out of 11 possibly steroid-induced remissions occurred after the disease had been present for over 12 months. There were no failures after splenectomy in patients who had had the disease for less than 12 months; only 7 out of 11 were successful if the disease had been present for more than two years. They recommend that in children up to 11 and perhaps in adults up to 24 years old it is worth waiting for 7–12 months to see if a steroid-induced or spontaneous remission will occur. If no remission appears, splenectomy should be carried out before the 12 months after onset of symptoms expires. On the whole they consider that their figures present "impressive evidence for the superiority of splenectomy in the treatment of unremitting idiopathic thrombocytopenic purpura as compared with steroid therapy."

All these results support contemporary ideas on the management of thrombocytopenic purpura. In the acute cases with short history and moderate to serious bleeding every effort is made to tide the patient over the crisis by giving steroids, such as prednisone in a dose of at least 50 mg. daily, and blood transfusion if necessary. A fair proportion of these patients, especially children, will go into remission and others will pass into the chronic stage. Splenectomy is avoided unless there are signs of incipient cerebral haemorrhage. In the less acute or the chronic cases steroid treatment is first given a trial for at least one month. If this produces a remission, with disappearance of signs and return of the platelet count to normal, and if the remission is sustained, no further treatment is needed. But if the platelet count falls again after steroid treatment has been stopped, whether or not fresh purpura appears, splenectomy should be considered and carried out within 12 months from the onset of the disease. This is especially necessary in young girls approaching the onset of menstruation and in young married women who may become pregnant. In others there is the danger of cerebral haemorrhage, and the papers cited show that this is a real if infrequent risk.

REGIONAL PERFUSION OF CYTOTOXIC DRUGS

The treatment of solid tumours by chemotherapeutic drugs has been severely handicapped by the limits of systemic tolerance to the agents concerned. For example, the toxicity of nitrogen mustards and related substances to the normal tissues of the haemopoietic system and gastro-intestinal tract has in general precluded the use of doses large enough to have a useful effect upon the neoplasm. It is to be hoped that this difficulty will eventually be solved by the discovery of more selective agents, but in the meantime the development of the technique of regional perfusion, first applied by O. Creech and his colleagues[1] in the United States, has given the

tumour inhibitors a new potential. Recently Mr. A. Lawrence Abel, of the Royal Marsden Hospital, London, visited the U.S.A. to study the techniques used there, and his report on them is published at p. 952 of this journal.

In this method the tumour-bearing region is isolated from the general circulation and perfused with the aid of a heart–lung machine. Provided the isolation is reasonably complete a much larger quantity of drug will reach the tumour than would be possible in the ordinary way. If leakage into the general circulation is not excessive (and this can be checked by means of dyes or radio-isotopes) the dose can be as high as the tolerance of the tissues served by the extracorporeal circuit will allow. Further publications by O. Creech, E. T. Krementz, and their co-workers[2 3 8] and reports from other centres,[4–7] mainly in the United States, have now appeared. One of the American workers who has perfused a large number of patients is J. S. Stehlin, of Houston, Texas, and in Britain, too, the technique is being used and developed, in particular at the London and Middlesex Hospitals. Most of the work has been done on limbs,[1 2 5 6] and the pelvis,[1 2 4] but cancers of the breast,[2] lung,[1 2] oropharynx,[2] brain,[2 7] rectum,[3] and ovary[3] have also been treated.

The choice of compounds used in regional perfusion is largely an empirical matter and has, with a few exceptions, been restricted to nitrogen mustard, L-phenylalanine nitrogen mustard, triethylene thiophosphoramide, and actinomycin D, but there is no obvious reason why the range should not be extended to include other compounds of established activity. A reliable way of choosing the best drug, or combination of drugs, for a particular tumour would be of great value. Krementz and his colleagues[8] have described a procedure which entails the assessment of the *in vitro* resistance to various agents of cells from the tumour to be treated, but the authors admit that the validity of the method is open to question. Sensitive methods are needed for estimating the concentration of an active drug in the circuit during the perfusion, for little is known about the uptake of tumour inhibitors by the tissues in these conditions. There are other questions to be answered. Is the total amount of a given drug a more important factor than its concentration in the circulating blood? What are the relative merits of chemically fast- and slow-reacting agents? Does oxygenation increase drug activity, or is this belief an unwarranted assumption based on certain well-founded experiences in radiology? Does selective heating of the tumour offer any advantages?

It seems reasonable to suppose that the selective delivery to a tumour of a relatively high dose of a cytotoxic agent might well produce impressive results. In practice, "impressive" seems perhaps too strong an adjective to apply in a general way at the present time, for the patient's response is not always satisfactory. Nevertheless a survey of the available data leads to the conclusion that the method of regional perfusion has given useful results in many cases. Though it is too early for a final assessment of results in the cases so far treated, there is little doubt that the new technique is well worth continued investigation, development, and application, both experimentally and clinically. Indeed, it deserves, and requires for its full exploitation, the attention of workers in several fields of scientific research.

[1] Creech, O., Krementz, E. T., Ryan, R. F., and Winblad, J. N., *Ann. Surg.*, 1958, **148**, 616.
[2] —— *et al.*, *Ann. Surg.*, 1959, **149**, 627; *J. Amer. med. Ass.*, 1959, **169**, 339; ibid., 1959, **171**, 2069.
[3] Reemstma, K., Ryan, R. F., Krementz, E. T., and Creech, O., *Arch. Surg. (Chicago)*, 1959, **78**, 724.
[4] Austen, W. G., *et al.*, *New Engl. J. Med.*, 1959, **261**, 1037.
[5] Monaco, A. P., and Austen, W. G., ibid., 1959, **261**, 1045.
[6] Saegesser, F., Hahn, C., Pettavel, J., and Livio, J. J., *Schweiz. med. Wschr.*, 1960, **90**, 11.
[7] Woodhall, B., Hall, K., Mahaley, S., and Jackson, J., *Ann. Surg.*, 1959, **150**, 640.
[8] Krementz, E. T., Creech, O., Ryan, R. F., and Wickstrom, J., *J. Bone Jt Surg.*, 1959, **41A**, 977.

DRUGS FOR PRIVATE PATIENTS

Free drugs for private patients are now in sight. Through their elected representatives in Parliament patients are at last making their voice heard in a growing volume of protest that promises should be kept, not broken, that the pledge given in Mr. Bevan's White Paper was backed up by what we all took to be a sturdy assertion of Conservative principles in the Right Road for Britain, 1949. For Mr. Walker-Smith to try to wriggle out of this at the meeting last week of the National Union of Conservative and Unionist Associations Central Council showed that he has inherited the Molotov mantle of some of his predecessors. It was a disappointing spectacle.

A recent leading article in *The Times* said roundly and encouragingly that this was a matter of equity. The support of *The Times* for the case of free drugs for private patients should have made Mr. Walker-Smith pause in his tracks and realize that the case was not a put-up job by a pressure-group in Tavistock Square. Then the rumour was put abroad in another newspaper that the doctors did not want private patients to have free drugs. But year after year the Representative Body of the B.M.A. has with huge majorities backed up this claim of private patients to take advantage of one part of the National Health Service—as they were promised.

One of the most curious arguments against giving patients the promised right to use one of the parts of the N.H.S. is that this would create two standards of practice, with the implication that private practice is somehow better than an all-in public practice. This

may or may not be true, but is an unjustifiable criticism of those doctors who prefer to work in a State service which puts the requirements for medical attention of a Cabinet Minister on exactly the same level as those of a cabinet-maker. Both have the right to the same penicillin when both have the same type of pneumonia. But the time of the one is more precious than the time of the other. There is no need to labour this point by citing the cases of eminent sick politicians, Labour or Conservative, who have not the time to queue in a doctor's surgery and therefore are prepared to pay for the convenience of time and place so that they may get on with their job in a way best suited to the exigencies of their position.

Another odd and equally illogical base of opposition is that granting private patients their right to free drugs would be to introduce a fee-for-item-of-service system instead of what—equally illogically—is regarded as the ideal system of payment by the capitation method. Why this fear of introducing, side by side with the capitation method, the fee-for-item-of-service method? The two methods exist side by side in Denmark. In Copenhagen the capitation method reigns supreme. Along with it there is a well-organized night doctors' service in which after a certain hour a different doctor cares for the patient treated by another doctor earlier in the day. This might be said to exemplify the principle of discontinuity of treatment. In other parts of Denmark —the agricultural districts—the method of payment is the fee-for-item-of-service, and the one and the same man looks after the same patient round the clock. In Norway the fee-for-item method prevails to the satisfaction of patient, public, politician, and practitioner.

Whatever the objections against giving free drugs to private patients, one consideration is paramount: the question of good faith. It is disappointing to witness the Government attempting to go back on a promise—a promise endorsed by a previous Conservative Minister of Health.

"GUT"

The new specialist journal with this title has now appeared, and successive numbers will follow at quarterly intervals. Published by the British Medical Association, it is the official journal of the British Society of Gastroenterology. It is edited by Mr. Harold Edwards, Dr. F. Avery Jones, and a committee of experienced consultants in this growing branch of medicine. The first issue includes papers concerned with such traditional themes of medical practice as "Early Investigations of Haematemesis," "Coeliac Disease," and "The Incidence of Chronic Peptic Ulcer Found at Necropsy." But, as a specialist journal should, it also takes the reader along more esoteric ways—"Serotonin, Bananas, and Diarrhoea" and "Intestinal Pseudo-obstruction with Steatorrhoea" (a hitherto undescribed syndrome). Since gastroenterology is a broad subject, of interest to many physicians and surgeons who would not claim to be specialists in it, the conclusion of the editorial foreword, by Mr. Harold Edwards, is worth quoting: "It is hoped that the usefulness of the journal will not, however, be confined to those whose sole interest lies in one of the many different facets of gastroenterology, but to all medical men, whether they be in hospital or general practice, who are responsible for the welfare of patients."

The annual subscription is £3, and orders should be sent to the Publishing Manager, *British Medical Journal*, B.M.A. House, Tavistock Square, London, W.C.1.

PROGOITRIN

The antithyroid activity of the thiourea derivative 1-5-vinyl-2 thio-oxazolidone, a substance more euphoniously termed "goitrin" by M. A. Greer,[1] has been recognized since it was originally isolated in 1949[2] from *Brassica* seeds and roots (swedes). Its role as a possible factor in the aetiology of non-toxic goitre has been considered to be minimal, as it is normally present only as an inactive precursor, "progoitrin." This was known to be converted to goitrin under the influence of an enzyme, which is destroyed by cooking. It has been thought, therefore, that swede and turnip roots, and cabbage, kale, and rape, from which goitrin has more recently been isolated,[3] would be goitrogenic only if eaten raw. Working with pure progoitrin, which he had previously been successful in isolating, Greer has now shown[4] that progoitrin has a demonstrable antithyroid effect when given orally to euthyroid or thyrotoxic individuals, and when given parenterally or orally to rats. *In vitro* studies with thyroid slices showed that goitrin, but not progoitrin, could completely block organic binding of iodine, so it would appear that hydrolysis of progoitrin to goitrin can occur in the body in the absence of the exogenously derived enzyme. In most people, therefore, eating cooked vegetables containing progoitrin should be just as likely to produce a goitre as eating them raw.

It is, moreover, probable that goitrin is excreted in the milk of cows fed on kale, so that an increasing number of dietetic influences may be concerned with the genesis of non-toxic goitre, the precise aetiology of which remains obscure. Certainly a number of factors other than deficiency of iodine and genetically determined inborn metabolic abnormalities remain to be investigated. The possibility of the persistence of antithyroid activity in cooked vegetables lends further point to the dietetic studies that have been and are being conducted in various areas. A second point of interest is that progoitrin may hold some promise as an effective antithyroid compound in the treatment of thyrotoxicosis, though the role of such drugs is perhaps less important now than when they were first introduced. Progoitrin gives a prolonged therapeutic effect from a single dose, and daily dosage with 1 g. had an effect comparable to that of 300 mg. propylthiouracil in a thyrotoxic patient. No side-effects were seen after oral progoitrin, and this work could well be a stimulus to the production and application of a therapeutically useful drug.

[1] Greer, M. A., *J. Amer. chem. Soc.*, 1956, **78**, 1260.
[2] Astwood, E. B., Greer, M. A., and Ettlinger, M. G., *J. biol. Chem.*, 1949, **181**, 121.
[3] Altamura, M. R., Long, L. Jr., and Hasselstrom, T., ibid., 1959, **234**, 1847.
[4] Greer, M. A., and Deeney, J. M., *J. clin. Invest.*, 1959, **38**, 1465.

ANTIBODIES AS RADIOTHERAPY AIDS

A few months ago an attempt to treat cancer by means of vaccines was discussed in these columns.[1] There are other ways in which immunology is taking part in the struggle against cancer. One of the most ingenious has been recently published[2]: it is a first stage in an attempt to use antibodies in the administration of highly localized doses of radiation to tumour tissue. It is not a simple attempt to carry the radioactive source itself into the tumour, but to carry in uranium-235 compounds which, under the influence of a beam of thermal neutrons from an atomic pile, release great amounts of energy "distributed among fission products of greater biological effectiveness than alpha particles. These fission products have a range of action of about 50 microns in tissues, by contrast to the range of about 9 microns from boron interaction with a thermal neutron."

Boron is already being investigated clinically for treatment of brain tumours, the method making use of its interaction with a beam of thermal neutrons.[3] But the energy released from it is low compared with that from fissionable substances such as uranium-235. However, compounds of uranium-235 are toxic, acting mainly on the kidney, so that, if they are to be used, they must be confined largely to the tumour site. The present work shows that this may be possible by combining the uranium compound with specific antibody and getting this complex to the tumour by means of perfusion. A biological model was used to demonstrate the possibility. To represent a tumour, a quantity of tetanus toxoid was injected into the calf muscle of a dog's leg. Tetanus antitoxin in a complex with uranium-235 was then perfused into the limb. After an hour's perfusion through the femoral artery and vein, the uranium-containing blood was washed out and the normal circulation of blood re-established. It was found that an amount of uranium sufficient for therapeutic purposes had been deposited at the site of the "tumour" as represented by the toxoid. Controls using a non-specific adsorbant, aluminium phosphate, showed no localization of the uranium-antibody complexes.

This work is still very much in the experimental stage. Many problems remain to be solved. The most serious one may turn out to be the production of true anti-tumour antibodies. Evidence for their existence cannot yet be regarded as convincing. The existence of antibodies against transplanted tumours has little relevance to primary tumours. The evidence for the existence of antibodies against primary tumours, such as it is, suggests that they are relatively impotent against the tumour. It may well be, therefore, that the only use that can be made of such antibodies is as carriers for anti-tumour chemicals or radiation-emitters. To this end the experiments discussed here are a courageous step, the achievement of usable uranium-antibody complexes being particularly noteworthy.

[1] *Brit. med. J.*, 1959, **2**, 750.
[2] Knock, F. E., *Surg. Gynec. Obstet.*, 1959, **109**, 445.
[3] Sweet, W. H., and Javid, M., *J. Neurosurg.*, 1952, **9**, 200.

PARENTAL CONSENT TO TREATMENT

Elsewhere in this issue (p. 976) Dr. P. H. Addison discusses the necessity for obtaining parental consent before an operation is performed on a child. His paper is mainly concerned with young people between the ages of 16 and 21, and he submits, on good grounds, that the patient's consent is all that is necessary provided he or she is over 16 and able to appreciate the nature and consequences of the treatment. With children under 16 the position is different. Unfortunately, conflicts between a doctor's desire to heal a child and the parent's right to decide what is best for the child's welfare are not unknown. The incidence of these conflicts is increased by the fixed objections of certain religious sects to medical or surgical treatment. In all such cases the doctor is placed in a dilemma, and any means of assisting him is worthy of close investigation.

The Sheffield regional hospital board last week approved a plan to set up juvenile courts in hospitals if the parents refused to give permission to an operation that seems urgently necessary. This would enable the magistrates, if they thought it desirable, to remove the child immediately from his parents, as being in need of "care and protection," and to put him into the care of a "fit person" who could give consent to the operation. Removal of a child under the age of 16 into the care of a "fit person" can be ordered by a juvenile court in a number of circumstances, one of them being where the person who has the care of him wilfully neglects him in a manner likely to cause him unnecessary suffering or injury to health.[1] A parent is deemed to have neglected a child in a manner likely to cause injury to his health if he has failed to procure, *inter alia*, adequate medical aid for him. Refusal to allow an operation may constitute wilful neglect of this sort. In deciding whether a case has been made out, the magistrates must be satisfied that the parent acted deliberately and that he failed to take such steps as a reasonable parent would take in the light of the ordinary experience of mankind. What is the reasonable course depends on the facts of each individual case: the magistrates must take into account the nature of the operation and the reasonableness of the parent's refusal to permit it.[2] The amount of information given to the parent by the child's doctor is clearly of the utmost importance in deciding whether the parent acted wilfully.

This jurisdiction can only be exercised if the child is brought before a juvenile court by either a local authority, or a constable, or an "authorized person." The most convenient course for a complainant who is not the local authority is to persuade the local children's officer to apply to the court on behalf of the local authority. The local authority is deemed to be a fit person willing to undertake the care of the child, and can give consent to the operation through the children's officer, since the person to whose care the child is committed has the same rights, powers, and liabilities as

[1] Children and Young Persons Act, 1933, s. 61.
[2] *Oakey* v. *Jackson*, [1914] 1 K.B. 216.
[3] Children and Young Persons Act, 1933, s. 75 (1).

if he were the parent. Unlike an ordinary magistrates court, a juvenile court may properly sit anywhere, so that there is no difficulty in convening the court in hospital if the child is too ill to be moved. However, the child's parent or guardian must, if he can be found and resides within a reasonable distance, be required to attend the proceedings, and his attendance can be enforced by summons or warrant.

There are two possible objections to this procedure on general principle. The first is that it is a further encroachment by "authority" upon the responsibility of the individual for his family affairs. But the jurisdiction is only exercisable if the parent has acted wilfully and unreasonably, and society has a duty to protect children against such parents. The second objection is that the judicial procedure is so speedy (moreover, the court is likely to be sitting in circumstances of some emotional tension) and the operation or other treatment so quickly performed that the parent has no effective right of appeal. If speed is essential to save life it is difficult to see how this defect can be overcome.

A technical difficulty may arise if the objection to treatment was made on religious grounds. Before making an order of committal to the care of a "fit person" the magistrates must try to ascertain the religious persuasion of the child and shall, if possible, select as a fit person someone of the same religious persuasion as the child, or some person who gives an undertaking that the child will be brought up in accordance with that religious persuasion.[5] If the child's religion forbids operation or other medical treatment an obvious difficulty arises. The crux of the matter is the words "if possible." If the local authority declines to undertake to bring the child up in that religion, the magistrate ought to look elsewhere for someone who will. The magistrates may be entitled to hold that anyone else who makes such an undertaking is not a fit person, and if they believe this they would be entitled to commit the child under the care of the local authority notwithstanding the authority's refusal to make an undertaking as to religious upbringing. However, the imperative terms of section 84 (7) of the Children and Young Persons Act (concerning the parent's remedy if the child is not brought up by the fit person according to his religious persuasion) are an indication that this interpretation of the words "if possible" is wrong in law. This is a point of law which may have to be settled by superior courts.

BLOOD AMMONIA IN EMPHYSEMA

There has been much interest in recent years in the blood ammonia, especially in relation to liver disease. Ammonia is produced during the breakdown of protein in the gastro-intestinal tract and by the kidneys and peripheral tissues. It is converted by the liver to urea, so that the amount normally present in the blood seldom exceeds 1 μg. per ml. If there is severe liver disease or an extensive portal collateral circulation, the level in the blood tends to rise, and high concentrations bear some relation to the clinical syndrome of hepatic coma. A characteristic sign of liver failure is the coarse flapping tremor of the outstretched hands, but this is not specific, since it may also be seen in both renal and respiratory failure.[1] Mental confusion and coma may be associated with chronic pulmonary disease, and it is of some interest that high levels of ammonia in the blood have recently been recorded in this condition.[2 3] R. Dutton and his colleagues,[2] for instance, found an average value twice as great as normal in a group of 34 patients. Since liver function was not impaired as judged by bromsulphthalein retention, liver damage as a cause of the rise in blood ammonia could be ruled out. It is more likely that the mechanism depends on some aspect of pulmonary insufficiency.

There is, for example, some relation between hypoxia and ammonia retention, since high levels of ammonia in the blood are found in emphysematous patients with a lowered arterial oxygen saturation, especially if this is accompanied by a rise in carbon-dioxide tension in response to a standard exercise test. It is also possible that elimination of ammonia from the lungs is impaired, as it is of carbon dioxide, because increase of the calculated arterial ammonia tension goes parallel with increase in carbon-dioxide tension. Unlike carbon dioxide, however, ammonia is not excreted solely from the lungs, so perhaps defective pulmonary excretion combines with hepatic impairment as a result of hypoxia to produce the rise in blood ammonia in emphysema. It has been suggested that in hepatic coma ammonia acts as a respiratory stimulant,[4] and in emphysema a positive correlation appears to exist between minute volume of respiration and the calculated arterial ammonia tension. It is interesting to speculate not only on the relationship of blood ammonia to the neurological features of emphysema, but also on how it may affect a respiratory centre no longer responsive to carbon dioxide.

DUKE OF EDINBURGH AT TORQUAY

All those intending to visit Torquay for the Annual Meeting of the B.M.A. in June will be delighted to learn that the President of the Association, Prince Philip, Duke of Edinburgh, will be present on Monday, June 20. Besides taking the chair at the presidential luncheon he will undertake other duties, including the induction of his successor as President, Sir Arthur Porritt. The Duke of Edinburgh's visit to Torquay has entailed some changes in the programme[5] of the Annual Meeting: full details are given in the opening page of the *Supplement* this week.

[1] See *Brit. med. J.*, 1958, **2**, 960.
[2] Conn, H. O., *New Engl. J. Med.*, 1958, **259**, 564.
[3] Dutton, R., Jr., Nicholas, W., Fisher, C. J., and Renzetti, A. D., Jr., ibid., 1959, **261**, 1369.
[4] Vanamee, P., Poppell, J. W., Glicksman, A. S., Randall, H. T., and Roberts, K. E., *Arch. intern. Med.*, 1956, **97**, 762.
[5] See *Brit. med. J. Suppl.*, February 13, 1960.

Clinicopathological Conference

A CARDIAC PROBLEM

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is the case of a Sierra Leonian (Case No. 190956; P.M. No. 8,035), who died in Hammersmith Hospital in congestive heart failure, for which clinically there were none of the usual causes. Dr. Maurice Campbell, senior physician of the National Heart Hospital, was guest speaker.

Clinical History

Dr. CHARLES FLETCHER: This coloured man, by occupation a surveyor, was aged 46 at the time of his death. He was well until five years previously, when he was living in Sierra Leone. He started running a public house and began to drink a pint (0.6 litre) of whisky and four pints of beer daily for two years. In October, 1953, he had a motor accident in which his chest was severely bruised. Four months later he began to notice exertional dyspnoea with orthopnoea at night and developed ankle oedema. A year later, in December, 1954, he came to England and was admitted to the National Heart Hospital, where he was found to have congestive cardiac failure and received routine treatment then and on two subsequent admissions in August, 1955, and May, 1956, when cardiac failure had recurred on discontinuing his maintenance therapy. He was first admitted to Hammersmith Hospital on October 9, 1956. No further relevant aspects of the history were discovered, but shortly before his death a relative reported that three sibs had died before the age of 40 with "large hearts."

On examination, he was orthopnoeic, with a frequent dry cough. He was afebrile, with a regular pulse of small volume, rate 96/min. The jugular venous pressure was raised 3–4 cm. above the sternal angle with prominent "a" and "v" waves. The blood-pressure was 110/90 mm. Hg. The apex beat was in the sixth space, 5 in. (12.7 cm.) from the mid-line with accentuation of left and right ventricular impulses. There was a third heart sound and a very soft apical ejection systolic murmur. There were scattered rhonchi in the lungs with rales at both bases. The liver was enlarged 2 in. (5 cm.) below the costal margin. There was ankle but no sacral oedema. There was albuminuria (0.5 to 1.6 g. in 24 hours) but no cells or casts.

INVESTIGATIONS

The chest radiograph (Fig. 1) showed generalized cardiac enlargement involving all the chambers. The lung fields were normal. On screening there was a local paradoxical pulsation on the left border of the left ventricle just above the apex. The E.C.G. (Fig. 3) showed signs of biventricular hypertrophy with possibly an old anterior septal infarct. The haemoglobin was 16.5 g./100 ml.; W.B.C. 7,000; E.S.R. 3 mm./one hour; serum proteins showed a slight increase of beta and gamma globulin fractions: blood urea 37 mg./100 ml.; serum cholesterol 345 mg./100 ml.; electrolytes normal.

SUBSEQUENT COURSE

On treatment with a low salt diet, digoxin, and mersalyl he lost his oedema and the venous pressure returned to normal. He was discharged on January 31, 1957, with only slight dyspnoea.

Two months later, on March 12, he was readmitted after a recurrence of dyspnoea. Clinical, electrocardiographic, and radiographic findings were as before. At first there was response to bed-rest and stricter restriction of sodium, but the patient remained breathless with a raised jugular venous pressure, persistent oedema, and albuminuria (1.7 to 4.3 g. in 24 hours).

On April 5 he had a sudden pain in the left hypochondrium attributed to a splenic infarct. He gradually went downhill and died in congestive failure on May 20, 1957.

Guest Speaker: Dr. Maurice Campbell

Dr. MAURICE CAMPBELL: I was going to ask, but I see that the patient was a native of Sierra Leone, not an Englishman who was out there. It is of course important when we come to discuss the most likely diagnoses, because there may be racial or geographical probabilities about heart disease in Africa, of which we are learning more. I thought that measuring the whisky consumption as a pint daily was characteristic of Hammersmith. What did he do with the rest of the bottle? In my experience it is a little unusual to get a combination of beer and whisky when they become excessive: it is generally one or the other. There seems to have been a period of two years of excessive consumption without anything in the way of symptoms.

ROLE OF TRAUMA

Then there is the interesting car accident, the common type where the driver has a blow on the chest from the steering-wheel. I think this is one of the commonest forms of traumatic heart damage in car accidents, so that we shall have to think about this as a possible explanation. We have no details about this, and, in particular, no evidence that he complained of more pain at that time than was natural. The gap between the accident and the first known symptoms was three months: nor was there any special history of anginal or of other chest pain. At the time of the first known symptoms he was already getting orthopnoea and oedema of the ankles.

The rest of the history is that of any form of congestive heart failure with normal rhythm. He had three admissions, first into the National Heart Hospital and later into Hammersmith, and he had orthodox treatment. As in many cases of congestive failure with normal rhythm, especially with a large heart, it is easy to bring about improvement, but the improvement is not very long lasting. In this particular case he lived about three years, and I think that most cases of this type live for a period of from two to five years with varying degrees of temporary improvement. So that

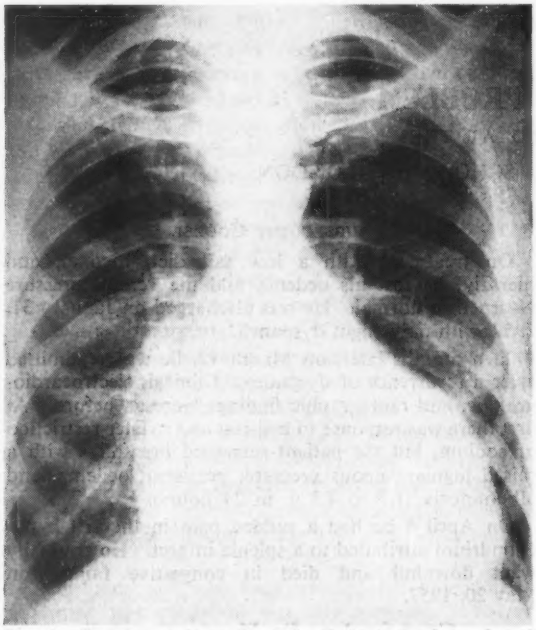

FIG. 1.—Postero-anterior radiograph of chest showing enlarged heart.

FIG. 2.—Barium swallow outlining the left atrium (lateral view).

when we consider the cause of his failure the latter part of the history is not much help to us. When a patient reaches the stage of congestive heart failure with normal rhythm, the course is much the same whatever the cause, so you do not get any particular help.

X-RAY AND E.C.G. FINDINGS

What help can you get from the other findings? There is not a great deal. You see an early radiograph (Fig. 1), which just shows a very large heart. There is not much to say about the left atrium (Fig. 2), for it has hardly more than a normal curve, considering the size of the heart. Later you see some improvement after treatment, and then, finally, a rather larger heart. Can we say anything about the weight of the heart from its size? The question of dilatation or hypertrophy is difficult to assess, and we do not know how much of the size is due purely to dilatation. The electrocardiogram (Fig. 3) provides some help by showing left and perhaps right ventricular hypertrophy as well. The apex beat was not, I think, described as being particularly forcible, but then he was not seen until he had developed heart failure, when that is not so reliable. I should have thought that this was a large heart, not one of the exceptional group where you are up to 800 to 1,000 g. in weight, but in the middle group below that, perhaps 600 or 700 g., but there might be more dilatation and less hypertrophy.

The electrocardiogram (Fig. 3) was reported on as some possible support for cardiac infarction. I would like to draw attention to a very important paper by Davies* on observer error in reporting on electrocardiograms—a paper that had its birth at Hammersmith. It is tedious to write down that an electrocardiogram might be normal though one or two points might suggest some coronary disease, and you feel that you are failing to be decisive, but it is the only way to write an accurate report. Very few cardiograms give you decisive answers on their own, and if you want

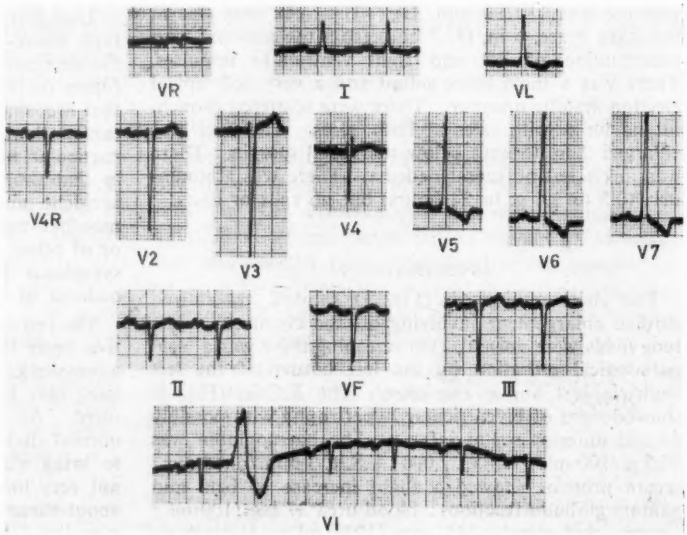

FIG. 3.—Electrocardiogram showing high voltage in leads V2, 3, 6, 7, and inverted T wave in V5, 6, 7.

*Davies, L. G., *Brit. Heart J.*, 1958, **20**, 153.

FIG. 4.—Heart. Left ventricle opened up. The mitral valve and inflow pathway is seen on the right, the aortic valve and outflow pathway on the left. The endocardium is partly covered with antemortem thrombus (T). In places the underlying endocardium is replaced by a thin layer of fibrous tissue (beneath T).

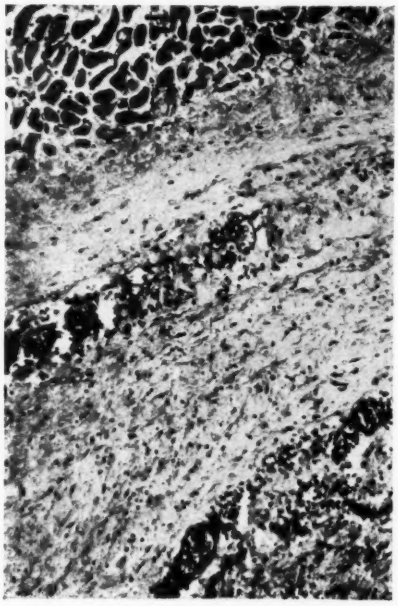

FIG. 5.—Inner part of the wall of the left ventricle underlying the mural thrombus. Heart muscle is seen above upon which is a layer of fibroelastic connective tissue traversed by distended capillaries accompanied by lymphocytes. (×112.)

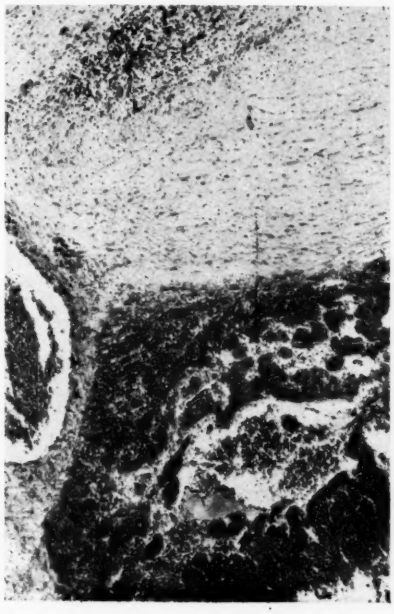

FIG. 6.—Mural thrombus in left ventricle (continued from Fig. 5). Myxomatous connective tissue above and organizing thrombus below. (×45.)

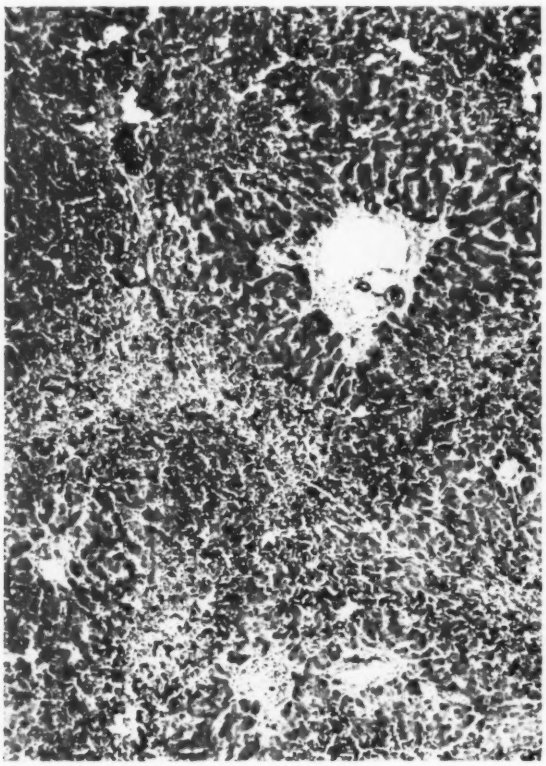

FIG. 7.—Liver. A large portal tract is seen to the right of the mid-line. The surrounding periportal parenchyma is well-preserved. The centrilobular zones beyond this show loss of hepatic cells and intense congestion. (×56.)

FIG. 8.—Reticulin preparation of Fig. 7 confirms the centrilobular collapse due to congestive atrophy of this zone. (×56.)

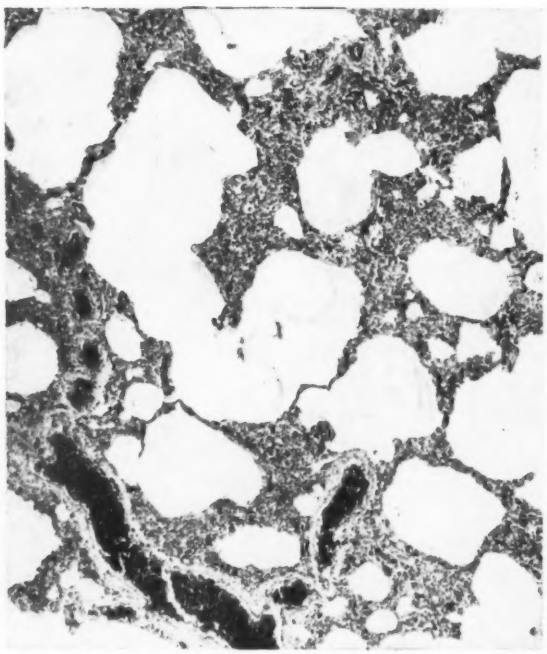

FIG. 9.—Lung showing congestive thickening of the interalveolar septa. (×56.)

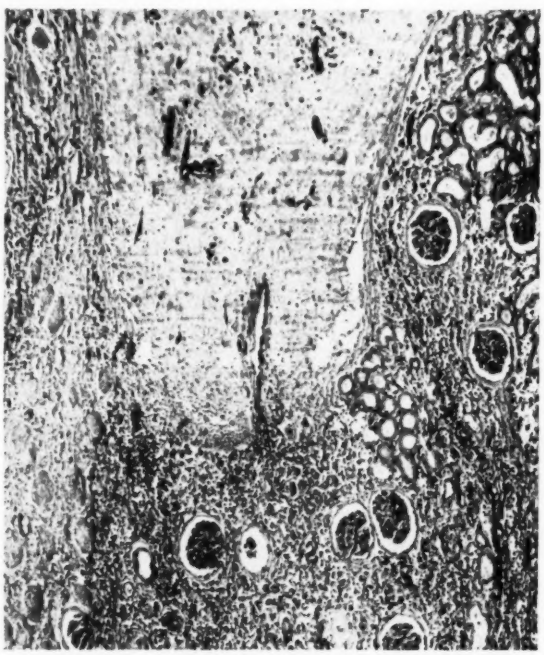

FIG. 10.—Periphery of kidney. A fibrovascular scar of an old infarct is seen replacing the subcapsular parenchyma. The parenchyma near by shows collapse and shrinkage of surviving renal tissue (×56.)

to be scientific about them there is often no way of reporting on them except by giving possible alternatives. Two cardiograms at a week's interval may prove a diagnosis of cardiac infarction. This is a good example where the changes suggest that there was something wrong, but it might have been almost anything. You see a slightly inverted T wave in lead I, there is genuine left ventricular preponderance judged by the size of S in V1 and R in V5, but the T wave changes could be due to left ventricular hypertrophy and strain, without any other changes. I do not think that there is much support for the diagnosis of infarction, either spontaneous or traumatic, after his accident. The other cardiograms show very little change except that a later one shows supraventricular tachycardia, possibly flutter, with 2:1 block.

As regards the biochemical findings, the serum albumin is just low but not very much: in a patient who has had albuminuria and failure for some time this occurs, so that I cannot draw any useful conclusion. The serum cholesterol is the only other significant finding, and it is only slightly high. This is found more often in the younger group of patients who have coronary disease, so that it might be used as a slight argument in favour of that.

Large Hearts in Failure

The real problem we are faced with, therefore, is the interesting one of congestive failure with a large heart, without the obvious reason for this—i.e., aortic regurgitation or hypertension. When we consider large hearts in general, I think over recent years there has been too much tendency to say that there must have been hypertension in the past and that the blood-pressure has come down. It is satisfying to be able to explain the reasons for cardiac hypertrophy, to say that it is always due to the extra work of overcoming a valvular obstruction or dealing with regurgitation or with high blood-pressure—and these are the things you should look for first—but it is not true that they are the only causes.

Very large hearts are found without these reasons, and I would like to know why you get this form of hypertrophy. It is not as easy to understand as the hypertrophy that follows hypertension, but there is too much tendency to say when you find a large heart that there must have been hypertension in the past. I do not think we have much evidence of earlier renal disease here. The albuminuria did not clear up entirely when his failure was least, and it could have been due to the failure. There was an intravenous pyelogram that suggested the possibility of pyelonephritic scarring, but I would not put this high as evidence. If, later, the pathologist can tell us that there was no significant renal disease, I think that past hypertension is ruled out. We have realized increasingly in recent years how large left-to-right shunts produce some of the largest hearts, but there is nothing whatever in the story or in the *x*-ray picture to suggest this. There is nothing in the radiographs, and no undue prominence of the aorta, to suggest that we missed the syphilitic case—and there was a negative Wassermann reaction.

Was it Cardiac Infarction?

We have really got four diagnoses to discuss here. First, was this a *traumatic or spontaneous cardiac infarct*? When you get failure after cardiac infarction it is more likely to start after four to six weeks than three months after the infarct. As you know, cardiac infarction is mainly diagnosed on pain: you get painless forms, but then you are making a less usual diagnosis, and I do not think that is likely. One support for it is the suggestion that there was some aneurysmal change in the left ventricle which, on screening, gave you paradoxical pulsation. But in the alternatives that we are going to consider there might have been some degree of local fibrosis in the heart which might have produced the paradoxical pulsation there. The electrocardiogram has been dealt with, so that, although I think cardiac infarction is a possibility, I do not favour this.

Endomyocardial Fibrosis

The second possibility is some disease of local geographical incidence, such as *endomyocardial fibrosis*. I do not know if Sierra Leone is a country where there are any common diseases of this type such as have been described in Uganda, but one is getting increasing knowledge from different parts of Africa about different diseases that we have not been familiar with. Very large hearts are not a special feature of endomyocardial fibrosis, and I do not think there is any particular point in favour of it.

Alcoholic Myocardiopathy

I think the choice is between this second alternative and a third one—*alcoholic myocardiopathy*—which I rather favour. It has become popular to minimize unduly the part played by the alcohol directly, and to say that it is vitamin-B deficiency. So far as I can gather from these notes, no physician at the National Heart Hospital or at Hammersmith treated this patient with vitamin B, so it does not appear that that figured largely in their thoughts in this case. I think alcoholic heart disease is much more common than you would gather from most books—and Brigden† in his St. Cyres lecture in 1957 on the myocardiopathies emphasized this and found a good many cases. They fall mainly into two types: (1) the very heavy beer-drinkers who probably have vitamin-B deficiencies and have many features of beriberi, and (2) the heavy spirit-drinkers who, I think, show primary myocardial changes. A bottle of whisky daily is about the amount that commonly produces this, and you will find them particularly—here I am quoting Brigden's recent experience—in two types of people, rich bachelors and those who have access to free alcohol. Among those people you find extraordinarily heavy spirit-drinkers, and many of them get heart trouble. I have found that auricular flutter was particularly associated with alcoholic heart disease; it is the only arrhythmia that would specially make me think about the possibility of alcohol. In these cases you can occasionally get reversion of quite advanced myocardial changes. The electrocardiographic changes found in this patient would, I think, do for an alcoholic myocardiopathy.

Familial Cardiomegaly

They would also do for a fourth and last suggestion, *familial cardiomegaly*. This is only suggested quite late by the story when his relatives said that three sibs had died at about 40. Family histories, when they depend on what relatives say, are sometimes difficult to rely on. The commonest cause of dying at 40 is hypertension, and this might make us think again of hypertension that was familial. But the fact that they

†Brigden, W. W., *Lancet*, 1957, **2**, 1179 and 1243.

said that these sibs died with large hearts before they were 40 does bring in the possibility of the rarer condition of familial cardiomegaly. There are some points a little against it: full bundle-branch block or at least wide-notched QRS complexes, very high voltage in the electrocardiogram, are common features, and none of these were found in this case; and sudden death is much more likely than death after increasing congestive heart failure for two years; but it is a possibility to be considered.

The pathologist may rule out the cardiomyopathies that I have discussed by finding something quite different. But, if not, can he be decisive in distinguishing between a cardiomyopathy produced by alcohol and one that is familial or due to some African disease? The histology of the large hearts of familial cardiomegaly has been rather varied, but there is general degeneration of muscle fibres with a good deal of hypertrophy and much vacuolation in the muscle fibres. I think that, if one found that, there would be a strong support for the familial form, but that an alcoholic cause is more likely. My diagnosis here would be that he had a very large heart and congestive failure from an alcoholic myocardiopathy, but that familial cardiomegaly, or a cardiomyopathy similar to but not the same as the endomyocardial fibrosis found in Uganda, is an alternative possibility.

Guest Speaker's Diagnosis

(1) Congestive cardiac failure, due to
(2) Alcoholic myocardiopathy
or ? Familial cardiomegaly
or ? An endomyocardial fibrosis.

Hospital Clinical Diagnosis

Professor J. MCMICHAEL: Dr. Fletcher, would you like to tell us what you thought the diagnosis was?

Dr. FLETCHER: The measurement of alcohol drinking in pints rather than in bottles may be due to the difference in the habits at Hammersmith and Guy's Hospital. We don't always finish the bottle.

We came to the same list of alternative diagnoses as Dr. Campbell, and dismissed traumatic infarction for the same reasons. We were rather more impressed by the endomyocardial fibrosis, and this was our first diagnosis. We were also impressed by the family history, and put familial cardiomegaly second. We did subsequently have a post-mortem report on one of the brothers, who apparently died from a combination of cor pulmonale and hypertensive heart failure with chronic nephritis, which rather spoilt the story, but when our patient died we didn't know this. We did not accept the diagnosis of alcoholic myopathy because of the steadily progressive course of the disease after the patient had stopped drinking.

Our diagnoses were:

(1) Endomyocardial fibrosis.
(2) Familial cardiomegaly.

Post-mortem Findings

Dr. I. DONIACH: The necropsy was performed by Dr. R. Cullen. The body was that of a man weighing 9 st. 12 lb. (62.6 kg.), height 5 ft. 11 in. (1.8 m.). There was ankle oedema, no finger-clubbing, no serous effusions.

The *heart* weighed 740 g., this weight including about 50 g. of antemortem thrombus. All chambers were dilated and hypertrophied. Dilatation was most marked in the left ventricle and hypertrophy in the right ventricle. A thick layer of antemortem thrombus, patchy in distribution, was adherent to the anterior, lateral, and septal walls of the left ventricle (Fig. 4). The endocardium underlying the thrombus appeared fibrous and moderately thickened; away from thrombus the endocardium was normal. The thrombus was restricted to the left ventricle. The tricuspid valve-ring, 150 mm. in circumference, and mitral ring, 145 mm., were grossly dilated. The aortic and pulmonary valves were normal. The coronary arteries were almost free of atheroma; there was no myocardial fibrosis. Microscopy showed hypertrophy of the myocardial fibres occupying the inner third of the left ventricle; the myocardial fibres of the outer two-thirds were not hypertrophied. No myocardial vacuolation or degeneration was seen. The left ventricular endocardium was normal in some areas. In others it was replaced by a band of young fibrous tissue, less than 1 mm. thick, rich in fibroblasts and in fine newly formed elastic fibrils. In its deeper layers this fibroelastic tissue contained scattered thin-walled blood vessels, siderophages, and lymphocytes (Fig. 5). This tissue resembled organized thrombus. Superficially (Fig. 6) there was a layer of recent antemortem thrombus showing organization at its site of attachment to the fibroelastic band.

The *lungs* (right 425 g., left 340 g.) showed brown induration (Fig. 9), and the *liver* (1,335 g.) a typical nutmeg pattern with loss of centrilobular hepatic cells and crowding of centrilobular reticulin fibres (Figs. 7 and 8). The *kidneys* (right 175 g., left 185 g.) showed scattered, irregular, ischaemic scars of total and partial infarction (Fig. 10) and a slight elastosis of interlobular arteries. There were numerous old and recent infarcts in the *spleen* (145 g.).

Pathologist's Diagnosis

The differential diagnosis was considered to lie between endomyocardial fibrosis (Davies and Ball*) and the condition labelled the heart disease of chronic malnutrition (Higginson *et al.*†). However, there was not the widespread endocardial fibrotic thickening affecting the inflow pathways of both ventricles, involvement of the atrio-ventricular valves, degeneration of subendocardial myocardium, or absence of peripheral emboli described by Davies and Ball in endomyocardial fibrosis. The findings in this case approximated more closely to those described by Higginson *et al.*, in whose 12 cases of "chronic malnutrition heart disease" emboli were frequent; fibrosis of ventricles was patchy, affected the outflow pathway, and was associated with overlying thrombus; and the atrio-ventricular valves were not involved.

Our final diagnosis was therefore cardiomegaly and heart failure of the type described by Higginson *et al.* as heart disease of chronic malnutrition.

Discussion

Professor MCMICHAEL: We have a representative from Johannesburg, Dr. Suzman. Would he start the discussion?

*Davies, J. N. P., and Ball, J. D., *Brit. Heart J.*, 1955, **17**, 337.

†Higginson, J., Gillanders, A. D., and Murray, J. F., ibid., 1952, **14**, 213.

HEART DISEASE IN AFRICA

Dr. M. SUZMAN: Clinically, I thought this patient did have what we call cardiovascular collagenosis, which is our local brand of endomyocardial fibrosis, and I think he fitted in very well with that diagnosis; the description agrees with the cases that we see in Johannesburg in both Whites and Africans. Although the majority of these cases occur in the African, the condition is also seen in white subjects. I have personally had quite a number of patients who would fit in with this particular clinical and pathological picture. I feel that the disease described in Uganda by Davies‡ is quite different from what we have seen here. For instance, we never see the obliteration of the cavities such as he described: the lumen of the ventricle may be obliterated almost entirely by the very widespread fibrosis, the valve being involved secondarily.

I cannot say anything about the cause of the disease. Very often just bed-rest, especially with the African patients, may lead to improvement. The patients may relapse and remit quite frequently until they go into an irreversible cardiac failure. On the other hand, in my experience, white patients who develop this disease don't do nearly so well. Once they go into failure, they don't seem able to come out of it. I think that very little is known about this condition anyway, and nothing about the cause.

We do see beriberi heart failure described occasionally in Johannesburg, also in both white and African subjects. They respond to vitamin B and have the usual haemodynamic characteristics of high-output failure. They are quite different from this type of condition in which there seems to be a low-output type of failure and which does not respond to vitamin B.

IMPORTANCE OF ALCOHOL

Dr. CAMPBELL: I would like to ask Dr. Doniach if he excludes alcoholism as a factor on his findings. And does Dr. Suzman consider alcohol an important factor in the Johannesburg cases? Just as there is reluctance in some circles to accept that cancer of the lung is caused by heavy cigarette-smoking, I think there is a similar reluctance to accept the importance of alcohol.

Dr. FLETCHER: We didn't pay so much attention to the alcoholic history here because it was so short and because he stopped drinking right from the onset of his symptoms. We gathered that he had given up his pub and been a complete teetotaller from 1954. We thought that if alcohol had been responsible he would have shown more improvement than he did. The same is true of the malnutrition hypothesis. I am very resistant to the idea that malnutrition has anything to do with this patient's disease, because he was a very well-nourished man. He was a surveyor in very good circumstances. He had not been under-nourished at any time, except just during the period of alcoholism, when he did neglect his diet.

There is one point I would like to ask Dr. Doniach about, and that is, what evidence was there at necropsy to confirm the cardiac aneurysm seen on screening, which of course was against the diagnosis of endomyocardial fibrosis and in favour of an infarct?

Dr. DONIACH: In a pretty careful description of the heart there is no mention of it. I think it would have been mentioned.

‡Davies, J. N. P., *E. Afr. med. J.*, 1948, **25**, 10.

NUTRITION OF THE ALCOHOLIC

Professor MCMICHAEL: The label "nutritional" has crept into medicine recently, and maybe it is creeping out again as we become more precise. Perhaps a fair amount of the energy requirements of allegedly undernourished people may be supplied by alcohol. Their nutrition is thus a little bit peculiar but not necessarily *mal*-nutrition.

Professor SHEILA SHERLOCK: I'm a little bit worried about the supposed lack of vitamin B in beer. Most of the better beers contain large quantities of vitamin B and quite a large amount of protein—yes, indeed, I wrote to Guinness and inquired. I would have thought that the alcoholic part, if you are going to blame alcohol *per se*, is going to be much more associated with spirit-drinking. And I'm a little worried altogether about this alcoholic heart failure. I think that many of the patients that have been described as suffering from alcoholic heart failure are in fact suffering from cirrhosis of the liver with a high cardiac output. It's a high-output heart failure following liver failure, and to diagnose a simple heart—the alcohol causing heart failure without the liver being involved—seems to me a little bit difficult, especially in a beer drinker.

Dr. C. PALLIS: I would like to endorse what Professor Sherlock has just said about beer. The development of "alcoholic neuritis" seems to depend on a high dietary ratio of non-fat calories to thiamine. Most beers provide both the calories and the thiamine: beer drinkers therefore rarely develop neurological trouble. Spirit drinkers are less fortunate.

Professor MCMICHAEL: There was a striking patient recently, who drinks a fantastic amount of beer. His consumption was of the order of 20 to 30 pints (11–18 litres) in 24 hours. He has been in heart failure three times in this hospital, where he gets better. He has really appreciated the cause of his trouble now and he's keeping off beer, with improvement.

Dr. SHERLOCK: He's got water intoxication!

A PHYSICIAN: I have had a little experience of beriberi amongst prisoners-of-war. I would like just to say that the people who went down with beriberi first were undoubtedly those who, before their capture, were heavy drinkers of beer as opposed to whisky.

RARER FORMS OF HEART DISEASE

Dr. FLETCHER: I was just going to ask Dr. Campbell why he ruled out amyloidosis in his list of diagnoses? We, I think, excluded this diagnosis partly on our failure to find other evidence of amyloid and its absence on liver biopsy, which we did for this reason.

Dr. CAMPBELL: I would say mostly on the absence of any obvious cause and on its relative rarity, although one was obviously dealing with something uncommon.

Might I make one further remark? It seems to me that my generation has been emphasizing the importance of aetiology in cardiac disease. It is difficult for you to imagine how much people talked about myocardial degeneration and myocarditis without any aetiology when I was a student. We have separated out coronary disease and hypertensive, thyrotoxic, rheumatic, and congenital heart disease, and, as always, we have become a little dogmatic about thinking that all heart disease is in those categories. Now we have got to pick out the less common forms of heart disease, and I think that there is a wide field for addition to the large common groups.

Professor MCMICHAEL: Could I ask one more question, I think of Dr. Suzman again, who has experience of these things in Johannesburg? It is said there that emboli commonly occur in 50% of the cases. How, in fact, do they come? Is thrombosis in the ventricle a common feature?

Dr. DONIACH: It was present in the ventricle in the one or two recorded cases.

Dr. SUZMAN: I showed a case like this with Dr. Evan Bedford in 1943 or 1944. It was a young man, and we eventually made this clinical diagnosis of so-called endomyocardial fibrosis. He ultimately died. We also thought he was a traumatic case, that he might have had an injury to his heart during a boxing bout. He died under an anaesthetic while receiving thiopentone. They quite commonly die suddenly during a minor operation. At necropsy he had a large area of fibrosis with thrombosis in the ventricle; he was a man in his early twenties, a white man.

Professor MCMICHAEL: We now thank Dr. Campbell for leading this discussion. His clinical approach was splendid, as nobody really knows the answer, either clinically or pathologically.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to the photographic department of the Postgraduate Medical School for the illustrations.

CHEMOTHERAPY FOR CANCER BY PERFUSION IN THE U.S.A.*

BY

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Introduction

In attempting to use cytotoxic drugs as a treatment for cancer they must be administered in such a way that they destroy the multiplying cancer cells without injury to the more delicate rapidly dividing marrow cells or other normal cells. If the drugs which are at present available and which are strong enough to inhibit cancer mitosis in the part of the body affected by the growth could be given without damage to the normal cells of the part, and especially without danger to the rest of the body, a new field of treatment would be attained. The method by which this is being accomplished is known as "perfusion."

Klopp *et al.* (1950) gave fractionated doses of nitrogen mustard to specific regions of the body by intra-arterial injections, with more pronounced effects on a tumour than had been possible by intravenous injections. They also suggested employing a heart–lung machine to maintain circulation in a tumour-bearing extremity during injection treatment with its circulation isolated. In the same year Bierman *et al.* (1950) found that if the nitrogen mustard was injected into an artery it was much less poisonous to the whole system than if injected into a vein. They also described methods of injecting a drug directly into the area of the growth. Other workers have conducted similar treatments for many types of cancer in different parts of the body. Bergel (1953), working at the Chester Beatty Institute for Cancer Research, Royal Cancer Hospital, reported the anti-tumour activity of phenylalanine mustard and Bergel and Stock (1954) described its preparation. Its L-isomer (melphalan or P.A.M.) has proved most active in this work. Later O. Creech, Jr., *et al.* (1958) reported their first results with perfusion by means of an extracorporeal circulation, and showed that they could give large amounts of a drug to an isolated part of the body under high arterial oxygen tension. Since December, 1957, similar perfusions have been undertaken at the M.D. Anderson Hospital and Tumour Clinic in Houston, University of Texas, by Dr. R. Lee Clark, Jr., Dr. John S. Stehlin, Jr., and their associates (Stehlin *et al.*, 1959).

*Report (here abridged) primarily written for the Board of Governors of the Royal Marsden Hospital after a visit to centres in the U.S.A.

Method

Perfusion entails:

(1) Pumps and oxygenator to provide a separate (extracorporeal) artificial circulation for the affected part of the body.

(2) Operation to isolate the diseased part from the circulation of the rest of the body.

(3) Electronic or other tests to make sure isolation is efficient.

(4) A high dose of anti-cancer agent or agents circulated long enough to be effective.

(5) Restoration to normal after washing out the drug from the region.

(6) Post-operative care, involving a knowledge of the special complications which may occur.

Apparatus

The apparatus required for a perfusion consisted essentially of two sigmamotor pumps to maintain the flow of the extracorporeal circulation and a Pulmo-Pak oxygenator (Abbott). This is a small disposable transparent plastic bubble oxygenator with a blood-reservoir capacity of 600 ml. Other pieces of apparatus required are varying sizes of catheters to cannulate the blood vessels, with plastic and latex tubings and stainless-steel connexions to complete the circuit. A source of supply of a gaseous mixture of 95% oxygen and 5% carbon dioxide is necessary to bubble through the oxygenator, the rate of flow being controlled by a flowmeter. A 250-watt infra-red lamp is used to warm the blood in the oxygenator to 100° F. (37.8° C.).

To isolate the extracorporeal circuit one or two tourniquets are usually needed. I saw in use an automatic tourniquet which is preset at the required pressure (for a thigh 500 mm. of Hg is advised), and by pressing a button at the required moment the tourniquet inflates.

Measurement of Leakage

The success or failure of perfusion depends upon accurate estimations of leakage from the perfused area into the main blood-stream. Special apparatus is required for testing the efficiency of the degree of isolation of the perfusion circuit—that is, detecting the degree of cross-circulation or "leakage." This involves the use of a radioactive iodinated serum albumin (R.I.S.A.) in the circuit, and its detection requires a scintillation probe linked with a counter and continuous recording device. The scintillation probe consists of a

photomultiplier tube (1,100 volts), a scintillation crystal 2 in. (5 cm.) diameter × 1½ in. (3.8 cm.) deep, and a pre-amplifier. Extra lead is used round this to avoid scatter from around and above, and it is rendered spark-proof. A gantry holds this heavy apparatus, which costs $500, over the base of the patient's heart and great vessels. It connects with a precision ratemeter which carries with it a Recti-riter recording device.

In conjunction with a calibration chart it is possible to assess the percentage of leakage—the leakage factor—between the two circulations. If such an apparatus is not available frequent estimations of blood levels of radioactivity must be made, but they take more time and are less accurate than the electronic apparatus.

Operation

The object of operation is to isolate the part of the body which contains all the cancerous process in such a way that the circulation of that part shall be separated as completely as possible from the circulation of the rest of the body. The completeness depends on the surgeon's knowledge of anatomy of the local arteries and veins, their branches and tributaries respectively, and all the routes by which they and their collaterals connect with all other vessels in the neighbourhood to reach the rest of the circulation. In addition to his skill as a surgeon it also depends upon the availability of plenty of time by himself and his assistants, to ensure that every possible collateral vessel is dealt with.

In the preliminary stages (removal of the primary growth, dissection of regional lymph nodes, approach to the vessels, etc.) care must be taken to secure every bleeding-point to ensure absolute haemostasis, because heparin is to be used.

Isolation of the distal part of a limb is relatively easy because only the main artery and vein need to be catheterized, and virtually all collaterals can be dealt with by a satisfactory tourniquet. In several cases there was no leakage at all.

To perfuse the whole of a limb including the axilla or the groin is not so easy without leakage, but in the case of the lower extremity the use of a Steinmann pin driven into the iliac crest at an acute angle and the application of a firm Esmarch bandage round the pin and the gluteal fold succeeded in about 90% of isolation. The pelvis, head and neck, breast, and liver all have their own special anatomical problems; they need long and tedious care for their isolation, because all collateral vessels must be occluded by multiple clips or ligatures.

Two tapes are passed round the main artery and two round the vein. The two artery tapes are threaded through two red rubber tubes and the vein tapes through blue ones. When all the anatomical work has been carried out and the wound rendered very dry, the patient is given heparin into the general circulation in a dose of 2 mg./kg. body weight (100 *B.P.* units per mg.).

Before any cytotoxic drug is introduced into a perfusion circuit careful tests must be made to determine what degree of leakage is taking place via collateral vessels between the isolated and the general body circulations. The scintillation counter is suspended over the base of the heart and great vessels of the patient, and counts per minute stabilized and recorded on the graph in an adjoining room. The physicist and two assistants were present and had the scintillation meter working before the anaesthetist injected 2 microcuries (R.I.S.A.) intravenously into the general circulation. It then took ten or twelve minutes to stabilize the readings of the scintillation counter for that amount of R.I.S.A. by graph and by formula. When the reading was constant and at a low level on the graph the surgeon proceeded with the insertion of the catheters into the taped main vessels. Meanwhile the bubble oxygenator had been primed with 500 ml. of blood to which 18 mg. of heparin has been added and the mixture of oxygen and carbon-dioxide bubbled through this blood at a rate of 4–5 litres per minute.

A small transverse incision is made into each vessel between the tightened proximal and distal tapes and a suitable catheter inserted past the distal tape, the surgeon using a larger-sized catheter for the vein to allow easy return of the blood from the venous side of the circulation.

Fifteen minutes after heparinization the primed oxygenator is attached to the two catheters, the preset proximal tourniquet blown up, and the two sigmamotor pumps switched on and synchronized. A solution of papaverine (180–300 mg.) is now injected into the arterial line of the extracorporeal circulation to produce vasodilatation. The rate of flow is adjusted to suit the anatomical site. In general a low rate of flow is maintained because of the difficulty of securing venous return and to allow better mixing of the drug with the tumour, a lower leakage factor, and a reduction of local and general complications.

After waiting a further 15 minutes for stabilization 20 μc. of R.I.S.A. was injected into the arterial side of the extracorporeal regional circulation. Now is the important time for the physicists to estimate by the scintillator the leakage-factor. After 15 to 20 minutes in more than one case which was having the lower three-quarters of the leg perfused there was no increase in the scintillation count, showing that the leakage factor was nil. In another case in which the whole limb from the groin was being perfused the count increased by only 5% in 15 minutes.

As the perfusion progresses in time so the leakage factor tends to rise, as it did at Houston in one case of extensive melanoma of the leg from 5% to 12% at the end of 45 minutes. This was considered to be a satisfactory isolation, and 100 mg. of P.A.M. was inserted proximal to the arterial pump and the whole limb perfused for upwards of 60 minutes. The level of blood in the larger section of the Pulmo-Pak must be kept constant in volume, flow rate, and temperature.

To protect the thyroid gland Lugol's iodine is given for two days before perfusion.

Dosage

The leakage is only one factor which regulates the quantity of drug which can be safely given. The second is the tolerance of the local tissues to the poisonous effects of the drug. At present the latter can be estimated only by experiments on animals and from clinical experience.

Where the leakage factor is nil or negligible, as in a limb, dosage depends solely on tissue tolerance. In other parts of the body as in aortic or carotid perfusion

the leakage factor and the local tissue tolerance have practically equal importance in determining the doses of drugs.

If the leakage factor is proved to be high (60%–100%) it is dangerous to give the recommended dosage. Either the project must be abandoned or a smaller dose used, after taking steps to protect the marrow by an autologous bone-marrow transplantation. 400–500 ml. of bone marrow is aspirated prior to the perfusion from the sternum and ilium, and diluted with 250 ml. of equal parts of Ringer's and acid citrate dextrose. Some hours after the perfusion the bone marrow is replaced.

Nitrogen mustard (HN_2) is introduced into the circulation in divided doses of 10 mg. at five-minute intervals and perfused for 20 minutes after the last dose has been added. Perfusion with a longer-acting drug such as phenylalanine mustard is continued for 60 to 90 minutes. This is given dissolved in propylene glycol 5 mg. of powder per 1 ml. of solution, and to this solution is added an equal portion of normal saline. The total amount of this drug is introduced at one injection.

Dr. Creech uses HN_2 or P.A.M. for limbs. HN_2 has also been used for bladder and breast. Thio-tepa seems best for ovarian cancer; for the pelvis generally P.A.M. or A.B.100, and for colon and rectum 5-fluorouracil. Actinomycin-D renders rhabdomyosarcoma more sensitive to *x* rays.

Restoration to Normal

When the treatment is finished the region is washed out with 500 ml. of dextran followed by 500 ml. of heparinized blood. This is carried out through a T-connexion inserted into the arterial side of the circuit. The blood containing the drug already in the circuit is thereby washed out and must not be allowed to re-enter the limb. The catheters are removed and the blood vessels repaired with silk sutures after testing the lumen with a Backus probe. The tapes and tourniquets are released and an anti-heparin drug such as "polybrene" (Abbott) 1 mg. per 100 B.P. units is given intravenously. Finally the wound is closed without drainage.

Dangerous quantities of drug in the general circulation can be counteracted with sodium thiosulphate.

Post-operative Complications and Care

The chief complications of perfusion are related to (1) local tissue tolerance, and (2) leakage factor.

If local tissue tolerance is exceeded, petechiae, erythema, mild oedema, tanning, blistering, or even gangrene may occur. Methyl prednisolone is advised to counteract the oedema.

If leakage is high, depression of bone-marrow occurs.

If the haemoglobin is less than 10 g. per 100 ml., give a blood transfusion. If the platelets are less than 30,000 per c.mm., transfuse with platelet-rich plasma. For leucopenia and fever give broad-spectrum antibiotics and cortisone.

Haemolysis of red cells may cause haemoglobinuria and anaemia.

All cases must therefore have daily blood counts, careful observation, and notes recorded on them.

Local tissue tolerance is a very individual, variable factor, but blistering of the skin and gangrene can occur. Gangrene may be produced by the trauma of handling the vessels or the use of the tourniquet, especially in patients with arteriosclerosis. These complications may precipitate the decision for amputation.

Complications are more likely to occur after a second perfusion, which should therefore be performed with smaller doses of drugs.

Results

The majority of cases so far perfused have previously had all modern methods of surgery and radiotherapy and have recurrence or extension of the disease. Results after only a little over two years cannot yet be assessed in survival figures, but I saw examples of the following: relief of pain in pelvic lesions, almost immediately; regression of recurrent and sometimes large and widespread melanomata; the saving of a limb which would, without perfusion, have required amputation; large inoperable tumours becoming small and operable.

Other values of perfusion may be: malignant cells in large tumours may be damaged enough to diminish their capacity to disseminate or become implanted; loose cells may be destroyed within regional lymphatics; as an adjunct to surgery, prophylactic perfusion of isolated organs commonly the sites of metastases may be feasible; a useful research method on the biological response of tumours to chemotherapeutic agents.

Recommendations

I feel that further research along these lines is highly desirable. Surgeons who have this type of patient to treat should, I believe, have ample and continuing laboratory accommodation for animal work to test the many drugs available. In the treatment of the large numbers of patients who might receive benefit much help will be needed from pathologists, physicists, nursing staff, and surgical assistants during long operating hours. Every facility for carrying out this work should be at the disposal of surgeons. Frequent consultations between all branches working on all types of cancer seem fruitful.

I was impressed with the simplicity, cheapness, and freedom from complications of the Pulmo-Pak. I was told that transistor scintillations should be cheaper and more mobile than valve equipment. I saw clear anatomical diagrams of difficult collateral circulations. I saw recovery rooms fully staffed and equipped with a visual E.C.G. attached to each serious operation case. A cardiac pace-maker was available for each patient. I gathered that ballooned catheters had not proved efficacious in preventing leakage in the aorta and vena cava in pelvic perfusion, but that, in Boston, work for liver perfusion was being investigated with these devices. I learned that work is being undertaken to assess the effect of "physiological" agents—for example, altered *p*H, variable glucose blood levels, high O_2 tension, and lactic-acid factor, both without

any drug at all and also with longer hours of perfusion with drugs.

At informal conferences I suggested that it might be possible to provide for a series of intradermal tests of a drug of varied strengths in an endeavour to assess pre-operatively local tissue tolerance; it might be worth while making a study of any possibly remaining collateral vessels by operative arteriogram taken on the table before the drug is perfused; something might be learned about cross-circulation if the leakage factor was tested in the opposite direction; vasodilators other than papaverine might be tried—for example, procaine; a model with two separate circulations might be made with a cross-connexion which could be opened and closed; not only might pumps, oxygenators, connexions, and electronic devices be tested, but the effects of different flow rates and blood-pressures be assessed, and, especially for beginners in this field, much animal work and time saved.

All who have had the privilege of seeing our American colleagues at work and partaking of their unending and overwhelming hospitality and friendship know how difficult it is adequately to express one's admiration and gratitude. I was recently privileged to spend about three days at New Orleans, Houston, Texas, and Boston, Mass. In each of these cities I received the greatest kindness and consideration from everyone I met.

At the first Dr. Oscar Creech is professor of surgery at Tulane University and the Charity Hospital of 3,800 beds. Among his many associates I met Dr. Krementz, Dr. Robert Ryan, Dr. Schramel, and Dr. Reemstma, and also the chief surgeon at the U.S. Marine Hospital, Dr. Lloyd Elliott. At the second I had a most friendly reception from Dr. Lee Clark, Dr. E. C. White, Dr. John S. Stehlin, Jr., and Dr. John E. Healey, and their many associates at the M. D. Anderson Hospital (350 beds).

At Boston I had recently met Professor Francis Moore, and now talked with some of his associates working on livers; also with Dr. Farber, and with him was working my colleague, Professor Franz Bergel, at the Boston Children's Hospital. I am very grateful to everyone.

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Nova et Vetera

NAPOLEON DISSECTED

Of the making of books on Napoleon there is no end. As early as 1824 Walter Scott complained of all the published books that he had to read before he wrote the emperor's life. Napoleon's medical history has also been studied in detail by many, and most authoritatively by Dr. Arnold Chaplin. Yet even now, as Mr. Kemble's study shows, new light can be thrown on Napoleon's maladies, especially from the standpoint of modern medicine.*

Napoleon Bonaparte had exceptional physical and mental energy. He could endure great fatigue, as in the Russian campaign, and sometimes would walk for five or six miles without feeling tired. He was frugal and temperate in his habits and an enemy to excess. But his health was far from satisfactory during the whole of his meteoric career. As a young man he contracted pulmonary tuberculosis. In 1789 he had prolonged feverish attacks when stationed at Auxonne and Valence; he suffered from cough in the Italian campaign and had haemoptysis in 1803. Antommarchi, at necropsy, reported signs of tuberculosis in the left side of the chest and small tuberculous cavities in the upper lobe of the left lung. Napoleon's son, the Duke of Reichstadt, died of consumption at 21 years of age. Napoleon's scabies dated from the siege of Toulon and persisted until his return from Egypt, when Corvisart cured him. His painful micturition has been attributed to stricture, but was more likely due to cystitis and stone. At necropsy several small stones were present in his bladder. Napoleon III, his nephew, had the same condition and died after an operation for it.

There is evidence that at infrequent intervals Napoleon suffered from angina and epileptiform attacks; the latter ranged from temporary loss of consciousness resembling petit mal to more prolonged seizures accompanied by convulsions. These attacks seized him at critical moments: for instance, at Aspern in 1809, where he was defeated by the Austrians; at Borodino in 1812, where he almost collapsed during the battle; at Düben during his wonderful campaign of 1813–14 against amazing odds, where, half-stuporose, he wasted four days when every hour was of importance; at Fontainebleau, when after taking opium he fell into a fit of prolonged stupor which led to the rumour that he had attempted suicide; and after Ligny in 1815, when he neglected to pursue the defeated Prussians and Wellington withdrawing from Quatre Bras. On the morning of Waterloo he slept when the heavy rain had ceased and it was imperative to strike swiftly. Mr. Kemble, on the evidence of King Jerome, ascribes the emperor's inertia here chiefly to an attack of haemorrhoids. At Paris and Malmaison he displayed apathy and indecision. He again abdicated, delayed to escape to the United States, and was taken a prisoner to St. Helena. Here he appeared to be in good health until the onset of the disease from which he died in 1821. Dr. Chaplin from the evidence at necropsy held that Napoleon died of cancer supervening on a chronic gastric ulcer; Mr. Kemble, from the clinical course of the illness, considers that it arose as a primary carcinoma of the stomach.

What was the mysterious illness which was partly responsible for Napoleon's downfall? Corvisart regarded the attacks as epileptic. Dr. Leonard Guthrie suggested that Napoleon suffered from some form of dyspituitarism which ended in hypopituitarism, as shown by his later obesity, etc., a view which Mr. Kemble favours. Such patients have a slow pulse and are subject to cerebral seizures. Napoleon's sustained vigour, energy, and intellect render this diagnosis doubtful. Madame de Rémusat said that Corvisart informed her that Napoleon had an exceptionally slow pulse, only 40 beats to the minute. Sir William Osler and Sir Arthur Keith held that Napoleon had Stokes–Adams disease, a view to which Mr. Kemble briefly alludes on p. 125. If so, the emperor's case was a mild one. The heart muscle was not involved extensively, and as a rule the syncopal and epileptiform attacks caused by cerebral anaemia were of brief duration, not severe, and infrequent. When complete heart-block has been established, the ventricles tend gradually to adapt themselves to the condition and the symptoms of the disease cease. This may have occurred in Napoleon's case, for he seems to have had few attacks after 1815 and his pulse-rate was quicker. Dr. Chaplin considered that in the absence of graphic records the diagnosis of heart-block must remain a supposition. This is true, but the slow pulse, if accepted, the anginal attacks, and seizures are significant. Mr. Kemble's book, based on the original sources of information, is a valuable contribution to Napoleonic history.

ARTHUR S. MACNALTY.

**Napoleon Immortal. The Medical History and Private Life of Napoleon Bonaparte.* By James Kemble, Ch.M., F.R.C.S. (Pp. 307+xi; illustrated. 28s.) London: John Murray. 1959.

Drug Treatment of Disease

AMOEBIASIS AND AMOEBIC DYSENTERY

BY

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As in all disorders of parasitic causation, recovery and identification of the causative parasite is essential to diagnosis. The presence of the infection can always be proved by competent examination of specimens of stool. During dysenteric attacks amoebae are swept out to the exterior in the loose stools; during intermissions cysts are passed in the formed stools. Treatment in the absence of a microscopical diagnosis is speculative; it is to be deplored in all but the most rare and exceptional case. In suspected amoebic dysentery not only must the parasite be identified but its presence must then be related to the history of the patient and his symptoms. A substantial proportion (probably about 5%) of people who have never been out of Great Britain harbour *Entamoeba histolytica* in the bowel, but disease, or symptoms, due to this infection are virtually unknown among them. These people have "amoebiasis," and they do not need specific treatment. Elsewhere in the world, particularly in the tropics, this parasite in some, but by no means the majority, of those harbouring it causes amoebic dysentery and its complications. In these areas therefore its presence must always be suspect, and should receive attention. This applies to persons returned from such areas to Great Britain, as infections in them may have been acquired overseas.

TREATMENT OF ACUTE AMOEBIC DYSENTERY

The acute clinical attack will always be effectively and rapidly stopped by the intramuscular, or subcutaneous, injection of emetine hydrochloride (sold in phials). The dose is 1 gr. (65 mg.) daily until the attack stops; injections over three to five days usually suffice for this; rarely are more needed. There is no point in continuing the emetine injections after arrest of the clinical attack. Emetine given in this way, however long continued, will rarely eradicate the primary intestinal protozoal infection. Its effect is clinical, not radical (parasitic), cure; therefore relapse of the disease is probable in the absence of additional treatment to ensure radical cure.

Though emetine is a toxic drug its potential dangers have been much exaggerated. Emetine injections should never be extended beyond a 12-day period. Patients being treated with emetine injections should *always* be confined to bed as a precaution against a possible effect of the drug on the heart. Early evidence of toxicity is a continuing rise in the pulse rate; E.C.G. changes take place; a peripheral neuritis, branny desquamation of the skin, and other signs of toxicity may develop later—but all these are temporary and rarely develop if the accepted therapeutic dosage is not exceeded. In practice the drug can be given as indicated without concern.

TREATMENT OF COMPLICATIONS

Acute Emergencies

The major complications of amoebic dysentery usually appear while clinical dysentery is not apparent. They are extra-intestinal and are acute emergencies which, if not specifically treated, are fatal. Amoebic infection can travel from the large intestine either by embolism in the portal circulation or by direct extension to surrounding tissues. In the former, and by far the more common, event an amoebic liver abscess results. If untreated this can extend to any organ or tissue adjacent to it; commonly it invades the diaphragm and right lung; sometimes it may spread further again by embolism. In the event of direct extension from the large intestine hard tumours (amoebomata), due to the amoebic together with a secondary bacterial infection, form on or adjacent to the large intestine. These tumours commonly are mistaken for neoplasms; often they are treated surgically without their causation being appreciated.

A colostomy leaking amoeba-laden matter is followed by amoebic infection of the wound tissues, with a spreading area of cutaneous amoebiasis under the dressing. There is a similar sequel to surgical drainage of an amoebic liver abscess, in the absence of specific treatment. In a continuously incontinent patient with clinical amoebic dysentery rapidly extending cutaneous amoebiasis may develop over the buttocks and perineum. These complications after surgical interference or neglect should not occur; unfortunately they do—but are rarely publicized. Very rarely there may be other complications, in the form of amoebic abscesses after embolism to the brain or other organs.

The specific treatment of extra-intestinal foci of infection with *Entamoeba histolytica* is simple and rapidly effective. Daily intramuscular injections of 1 gr. (65 mg.) of emetine hydrochloride over a period of 12 days almost unfailingly sterilize all the extra-intestinal lesions of their amoebic infection and lead to their resolution in a dramatic manner. There should be no delay in specific treatment of extra-intestinal amoebiasis, and it must never be omitted whatever other line of treatment is followed. In its absence the amoebic colliquative necrotic process continues to extend.

Liver Abscess

For treatment of an amoebic abscess of the liver there is an alternative to emetine. This is the anti-malarial drug chloroquine. The dose is an initial one of 1 g. of the salt given orally; this is followed by 0.5 g. daily for six to eight days. Such a patient may be treated with emetine and chloroquine concurrently; there is no reason why this should not be done. Chloroquine has no action on amoebae other than those in the liver. Toxicity due to chloroquine is usually first manifest by visual defects; if they occur the drug should be stopped and they will resolve.

When the extra-intestinal amoebic infection has been cleared the persisting primary bowel infection with *E. histolytica* must not be forgotten. If neglected, a recurrence of complications is likely. Successive

amoebic liver abscesses developed in ensuing years in one patient when this elementary fact was overlooked. A full course of treatment to eradicate the primary intestinal infection therefore always must follow the satisfactory outcome of treatment of any complication of amoebiasis.

RADICAL (PARASITIC) CURE OF INTESTINAL INFECTION

Claims are made for many proprietary drugs now on the market for this purpose. They are given orally, and their action is specifically on the parasites. But in addition to this, oral treatment with certain of the antibiotic drugs (e.g., the tetracyclines, erythromycin, spiramycin, and others), themselves not amoebicidal, may be followed by disappearance of the parasitic infection. These antibiotics are believed to alter the associated intestinal bacterial flora essential to the survival of the amoebae in the large intestine. There are some antibiotics which are directly amoebicidal (e.g., fumagillin) *in vitro*, but therapeutically they have proved disappointing, and in the case of fumagillin undesirably toxic. Paromomycin (" humatin ") is the most recent of the antibiotics claimed to be amoebicidal, and it is stated to be free from toxic side-effects in the advocated dosage.

E.B.I.

The most consistently effective of the directly amoebicidal drugs is emetine bismuth iodide (E.B.I.); this was brought successfully into use during the first world war. Its activity so far has not been equalled by that of any other drug yet available, and it is the basis of the treatments advocated by most British physicians. The dose is 1 gr. (65 mg.) given orally thrice daily, and it alone may be given daily over 10 days; together with other drugs similarly; or on alternate days together with other drugs over two or three weeks. E.B.I. if taken in an unprotected form will be vomited; it is therefore given in enteric-coated tablets which liberate their contents after three or four hours' digestion. Some nausea even then will be experienced; this is cerebral and due to absorption of the drug; with habituation the side-effects lessen. With E.B.I. as the basis of drug treatment, radical cure of an intestinal amoebic infection can be expected in over 90% of patients.

Among the older directly amoebicidal drugs are a variety of arsenicals (e.g., " milibis ") and iodo-oxyquinolines (e.g., " embequin "). Any of these when given alone is unsatisfactory, in that it will not sterilize the intestinal amoebic infection consistently and in a satisfactory proportion of cases. If used at all, these drugs should be given concurrently with E.B.I. as a supplement to it; profitably they can be given orally on alternating days with E.B.I. over a period of three weeks, so lessening the digestive upset caused by the E.B.I. Chiniofon, a water-soluble (4%) iodohydroxy-quinoline, can with benefit be given as a retention enema on days alternating with E.B.I. treatment, and after an enema clearance of the bowel. Its action is both directly amoebicidal and antibacterial; it is not absorbed to a material extent and is non-irritant; it promotes cleansing and healing of gross lesions in the large bowel. The arsenical drugs must be used with caution, and be stopped promptly on the appearance of any skin rash. This is rare, but if the drug is continued thereafter serious toxicity with an exfoliative dermatitis and liver damage may attend their use.

The newer amoebicidal drugs include a series of phenanthrolines (e.g., " entobex "), dichloroacetamides (e.g., " mebinol," " entamide "), and diethylaminocresols (" camoform "). All these are given orally. Reported trials leave the impression that no drug of these series has been proved the equal of, much less superior to, E.B.I. in ensuring a consistently high rate of radical cure of the intestinal amoebic infection. They have merit in their being free of toxic side-effects.

Antibiotics

Many antibiotics when given orally alter the constitution of the intestinal flora, and may consequently lead to the disappearance of an intestinal *E. histolytica* infection. The tetracycline antibiotics are good examples of these, and given alone—oxytetracycline (" terramycin ") or chlortetracycline (" aureomycin ") 0.5 g. 6 hourly for 10 days—will be followed by disappearance of the parasitic infection in about 60% of patients so treated. But this achievement is equalled by that of most of the amoebicides mentioned, and is much surpassed by that obtained by E.B.I. treatment. Needless antibiotic treatment in general is to be deplored, and so in this condition it is better avoided. Where the antibiotics do play a most valuable role is in those extremely rare cases which prove refractory to sterilization by repeated treatment with E.B.I. in conjunction with other amoebicides. Repetition of such amoebicidal drug treatment together with the administration of a tetracycline antibiotic has most effectively cleared these rare and unusual cases.

Harmful Treatment

Finally, and emphatically, long-continued drug treatment, whether sustained or intermittent, for " amoebic dysentery "—usually unsubstantiated by microscopical diagnosis—is unjustified. The infection is readily eradicable by a short intensive course of treatment. Indefinite prolongation of this can do no more, and it is harmful to the patient both physically and psychologically.

" Denman's pupil and son-in-law was Sir Richard Croft. He was the man in charge of the confinement of Princess Charlotte. A full account of this was the subject of Sir Eardley Holland's William Meredith Fletcher Shaw Memorial Lecture in 1951, and was based upon Sir Richard Croft's full notes of the case which had only recently been discovered by Croft's great-great-grandson, Major Richard Croft. Princess Charlotte of Wales was the only legitimate grandchild of George III, in spite of the fact that he had seven sons and five daughters. She was married to Prince Leopold of Belgium, and on her and her alone the future of the monarchy depended. The unfortunate Princess had a long labour of 54 hours, 24 of which were occupied by the second stage, and the head was on the perineum for five or six hours. Nothing whatever was done to assist delivery, and the baby—a boy—was eventually delivered without assistance. It had been dead for some hours. Charlotte died about five hours after the birth of the baby from post-partum haemorrhage. Croft never got over the shock, and shot himself three months later. Holland blames the ultra-conservative teaching of the time widely accepted as a result of Denman's writings; for example, ' Denman's Law ' laid down that the head must be on the perineum for six hours before forceps should be applied. The death of Princess Charlotte changed obstetric teaching, and marked the end of the ultra-conservatism of Hunter, Denman, and Croft." (*Proceedings of the West London Medico-Chirurgical Society, 1958*, Presidential Address, October, 1958, by Mr. Arnold Walker.)

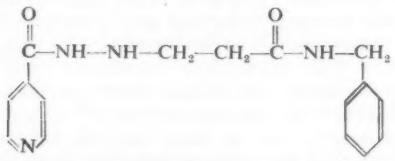
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Nialamide

"Niamid" (Harvey Pharmaceuticals).

Chemistry.—This is 1-[2'-(benzylcarbamyl) ethyl] 2-isonicotinoyl hydrazine and has the following structural formula:



Pharmacology.—Nialamide is a potent monoamine oxidase inhibitor. Further, it reverses the action of reserpine, which in high doses produces in animals a state of immobility and apathy. Both laboratory and clinical studies have shown nialamide to be relatively non-toxic and free from undesirable somatic effects.

Therapy.—Nialamide has been tried as a treatment for depressive states largely on account of its pharmacological properties. However, there is not necessarily any connexion between amine oxidase inhibition and therapeutic antidepressive properties. The identification of such properties with "reserpine antagonism" and the description of the usual effects of reserpine on animals as "depressive" is unwarranted, even though it is very likely that reserpine occasionally produces in human beings a state clinically indistinguishable from depression. Clinical studies bearing on the matter, so far published, are inadequate. In none is the effect of nialamide compared with E.C.T., at present the most effective treatment of depression, or with a placebo (a necessary precaution for securing significant results because depressive states are mainly self-limiting).

With these reservations in mind it can be said that most clinical observers report about half their depressive patients improved on nialamide. The depressive syndrome, when it is prominent, is also relieved in some cases with other diagnoses (e.g., schizophrenia, arteriosclerotic dementia). An increase of anxiety is a troublesome feature frequently commented on, for which a sedative or tranquillizer has been successfully given. The average quantity of nialamide administered is 75–100 mg. daily in three or four doses.

Nialamide is also reported as giving symptomatic relief to some patients with angina pectoris. Here the dose was 37.5–150 mg. daily in three doses.

Toxic Effects.—None serious have been reported. Side-effects are infrequent, but headache, dry mouth, sweating, dizziness, constipation, and blurred vision occur.

N.H.S. Basic Price.—100 25-mg. tabs. for 41s. 8d.; 100 100-mg. tabs. for 141s. 8d.

So far as foreign matter was concerned, of seven complaints investigated, four dealt with bread, two pasteurized bottled milk and one mussels in vinegar. Streaks of machinery grease, bakery dirt, sooty matter found to have originated in an electric blower, and a small nocturnal beetle (*Alphitobius diaperinus*) were identified in the bread specimens. One sample of milk contained about 2% hypochlorite disinfectant and another about 10% extraneous water. The mussels were suspect because of certain green matter present; similar complaints have been reported on other occasions—the green matter is in fact normal and represents part of the contents of the digestive system of the creature. (A. H. Coombes, (Birmingham City Analyst) *Report for the Fourth Quarter*, 1959.)

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

"Imferon"

SIR,—In your leading article entitled "Carcinogenic Risks of Iron-Dextran" (March 12, p. 788) you refer to published results of our work which was completed over two years ago. These investigations have continued, and we would have welcomed the opportunity to provide details of our later findings[1–5] had we been so requested. Perhaps at this stage I may be permitted to remedy this omission, and to comment on the scientific aspects of the questions raised, by a summary of the conclusions from our own experimental work, much of it as yet unpublished.

Let us consider the facts established so far. It is clear that in rats given the lower of Richmond's[6] two-dose ranges (a total of ca. 475 mg. Fe injected into one site) our results are substantially similar. But at lower doses, which still exceed 50 times the total human clinical dose on a weight basis, the incidence of tumours drops sharply to become comparable with, or even lower than, published figures for tumours obtained in a similar manner by repeated subcutaneous injections of glucose, fructose, arachis oil, and many other "innocuous" materials.[7–9] In our mice the incidence of tumours has been very much lower than in the series reported by Haddow and Horning,[10] a fact which may be attributable to strain differences. The mice we employed were stock albino, whereas those of Haddow and Horning were males of a strain exhibiting a high incidence of mammary cancer in the females.[11]

Haddow and Horning consider that the injection-site sarcomata induced by iron-dextran constitute yet another manifestation of the carcinogenicity of iron. In interpreting these observations the authors conclude that the tumours are directly due to the local action of the iron-dextran complex, and are "decided primarily by the absolute amount administered and only secondarily, if at all, by the relation of this to the total body weight." This interpretation of the facts completely disregards the grossly abnormal changes which invariably develop at the site of repeated massive injections of iron-dextran, whether or not sarcomatous change subsequently ensues. (It must be stressed that these local lesions are completely absent in man and animals when iron-dextran is administered in therapeutic doses on a weight-for-weight basis.) Equally, the profound systemic effects which accompany such massive iron overload are ignored by these authors. We have devoted much research to these aspects, which we believe to be of fundamental importance in the assessment of the significance of the whole phenomenon in relation to the therapeutic use of iron-dextran.

We have described[12 13] the sequence of changes in rat muscle following the injection of a single large dose of iron-dextran (equivalent to the total therapeutic dose on a weight basis). The mechanism of absorption involves the rapid lymphatic removal of the majority of the injected material before local macrophage accumulation reaches appreciable proportions. When massive doses are administered repeatedly into the same site this absorption mechanism is overwhelmed and residual siderophage accumulations assume ever-increasing proportions. Widespread necrosis of muscle, followed by its partial or complete replacement by adipose tissue and masses of siderophages, becomes one of the most striking features of the lesion artificially created under these extreme experimental conditions.[2] Repeated subcutaneous injections into the abdominal wall of mice lead to very similar but even more drastic changes. These lesions do not occur with doses of iron-dextran nearer the therapeutic level.

The view that in such experiments the dosage should not be related to the size of the animal, which merely consists of an injection site with a body attached, appears to us to be untenable. The *bulk* of the local tissues available for absorption of any given dose is a crucial factor. The damage resulting from a proportionately large dose in the circumscribed area of abdominal wall of the mouse or thigh muscles in the rat interferes with the local absorption mechanism. The same dose administered to a larger species does not produce a local lesion. Therefore it is impossible to disregard the total muscle mass in considering the dosage employed.

Profound systemic changes also result from massive overloading with iron. These include reticulo-endothelial stimulation similar to that brought about by high doses of zymosan[14] (but maintained for a longer time); altered tissue enzyme activities[3,4]; manifestations of loss of antioxidant capacity—signs of vitamin E deficiency,[15–17] increased formation of tissue peroxides, and development of lipofuscin polymers in large amounts; enhanced hepatic susceptibility to toxic and adverse nutritional influences.[1] These systemic disturbances are not encountered until "metabolic swamping" with iron has been achieved. It is important to record that the altered enzyme activities, the accumulation of tissue peroxides, and the lipofuscin polymers are also present at the injection sites. Whether or not one considers the systemic changes outlined to be of importance, there is no escaping the fact that they are also present in the siderotic local tissues from which sarcomata arise.

Haddow and Horning [10] stress the "outstanding carcinogenic potency" of imferon. What their work, like that of Richmond,[6] clearly demonstrates is the remarkably low chronic toxicity of this iron complex, which affords an opportunity to administer doses of iron on a scale that is impossible to duplicate by any other means. Thus Haddow and Horning's two series of mice received 130 and 450 mg. Fe *per mouse* as imferon, whereas with ferrous sulphate the total dose of iron was 8.0 mg. Fe (1 fibroma), with ferrous lactate 14.1 mg. Fe (1 sarcoma) and ferrous gluconate 7.5 mg. Fe (1 fibroma, 1 thymoma, 1 thecoma). It should be remembered that the total body iron of the normal mouse is 2 mg. In a note added in proof the authors refer to lower-dosage experiments in which a sarcoma appeared after about 35 weekly injections of 0.05 ml. iron-dextran—that is, approximately 90 mg. Fe per mouse. This is still about 70 times the total clinical dose on a comparative weight basis.

It is surprising that in your leading article only the results in rats and mice are quoted and no reference is made to the important species variability in tumour yield. Thus in the rabbit no tumours were obtained; in the hamster, one out of fifty; and none in the guinea-pig. All these species received massive overdoses of iron-dextran.[10]

Finally, the question may be asked: Has our emphasis on the study of pathogenesis afforded any hint of the manner in which these tumours arise? Here we must necessarily extrapolate from known facts to achieve a working hypothesis. Repeated trauma, muscle necrosis, and chronic inflammatory change caused by injections of a wide variety of chemical agents, including hypertonic saline and glucose, into the unstable subcutaneous tissues of rats[18] and mice can lead to the production of sarcomata. Why is the yield of tumours variable and often low? Possibly because the body's defence mechanisms—to put it no more specifically than that—eliminate most of the tumours at some early stage in their development. Zymosan in low doses stimulates these defence mechanisms to eliminate implanted tumours, but in high doses it has the opposite effect.[19] As we have seen, the reticulo-endothelial effects of massive doses of iron-dextran are similar to, but more prolonged than, the action of zymosan, and it is conceivable that swamping the body with iron serves to promote the local growth of tumours which would otherwise not have survived. Thus the development of sarcoma may depend on a massive siderotic local lesion coupled with systemic swamping of the animal with iron-dextran or other agent capable of stimulating the reticulo-endothelial system.

We have tried to apply this working hypothesis in various ways. An experiment in which the first tumour has now appeared after nine months is one in which cell-free filtrates from rat sarcomata induced by the Richmond technique have been injected subcutaneously into the abdominal wall of normal rats, and of rats which had been massively overloaded with iron by intramuscular injections into the hind limbs. The sarcoma arose in an iron-laden rat. It was situated in the subcutaneous tissues of the abdominal wall at the site of injection of the cell-free filtrate and well clear of the iron-injected muscles. This result is reminiscent of the fibrosarcomata obtained by Salaman[20] following the injection of cell-free filtrates of leukaemic tissue into mice.

The assessment of the risk involved in the clinical use of imferon can best be made by comparing the histological appearance of human tissues after imferon with the observations in animals. We have examined skin sections taken from a patient at various times following single *subcutaneous* injections of 100 mg. Fe as imferon. We can confidently state that 23 days after such an injection all that remains at the site is a small number of siderophages around hair follicles, sweat glands, and blood vessels—probably no more than one would find as an aftermath of a haematoma. Equally, skin and subcutaneous tissues at sites of imferon "staining" show a surprisingly small residuum of iron in phagocytes and connective-tissue cells. We have also examined injection sites in human muscle, and again there were no changes in any way resembling the muscle destruction with replacement by adipose tissue and the siderotic masses seen as a result of massive overdosage with imferon in rodents.

A critical examination of all the facts concerning the mode of development of the siderotic lesion which is only created under drastic experimental conditions convinces us that, in the absence of such a lesion, sarcomatous change is in the highest degree unlikely to develop. Since there is no evidence that a lesion of this kind is ever formed in man following the clinical use of imferon, it must be concluded that there is no risk of sarcomatous change after imferon therapy.—I am, etc.,

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SIR,—Your rather alarming leading article on the carcinogenic risks of "imferon" (*Brit. med. J.*, March 12, p. 788) raises several points on which G.P.s like myself need guidance.

Fourteen years ago, while working in an obstetrical unit, one acquired the habit of giving "ferrivenin" (saccharated iron oxide) intravenously, and continued to use this method in practice. When imferon came on the market one soon observed the large painful swellings in patients' buttocks after hospital treatment and also the unsightly staining that appeared at the natal fold, even when the injection had been given correctly. This method has been used only once by myself, and instead intravenous injection was continued, using imferon. The usual dose given is 10 ml., using the technique of intermittent dilution with blood. The only reaction seen has been blushing, particularly of the neck and face, which passes off in a few minutes. Both my partners have adopted this method in the last six months and their experience has been similar.

It would appear from the evidence that the myosarcomas occur only as a local reaction, presumably due to the persisting deposit of iron hydroxide. It has been established that the absorption of iron from the intestines is in inverse proportion to the degree of anaemia. This paradoxical and teleologically speaking illogical phenomenon is pertinent—the more so as it is said that the iron reserves of the liver cannot be replaced even after intensive and prolonged oral treatment. Are we to conclude that imferon cannot be used intravenously, even though there is no evidence that it can act as a systemic carcinogen? Does the same objection apply to ferrivenin? This substance was used most successfully for years and the question of local carcinogenesis did not arise as it is far too irritant for intramuscular injection.

An interesting case in my practice is that of a premature infant who was kept in hospital for some weeks. On returning home it had a very large hard swelling in the left buttock due to injections of imferon. The mother was worried by its size, the child's crying when laid on that side, and the fact that the child never voluntarily used that leg. The mother was reassured; the swelling, although diminishing, persisted. At 18 months, when the child began walking, the mother noticed he fell over to the left. Examination showed this left leg to be half an inch shorter than the right and proportionately small in all dimensions. The child now runs about normally, but the disproportion persists. A paediatric consultant considered this was due to coincidence, but could give no reason for the abnormality. Now at 2 years 4 months the child still has a hard nodular swelling in the buttock one and a quarter inches in diameter which is attached in places to the skin. At the areas of attachment the skin is thin and brownish-black in colour.

In view of the present finding should this tumour be excised as a prophylactic procedure? Should the persisting nodules in the buttocks of adults be also excised? I would be grateful for comments on these matters.—I am, etc.,

Northwich, Cheshire. E. DESMOND DILLON.

SIR,—In view of the present concern about "imferon" (March 12, p. 788), I think it is of interest to record an unusual side-effect of this preparation.

Just over a year ago a patient was admitted to hospital after a course of imferon injections into the buttocks. A raised, red, oval lesion about six inches long and three inches across had developed over the lumbar spine. It was thought to be a cellulitis, and cleared up after penicillin and bed rest. This case was described at a clinical meeting when a similar case was also presented. The aetiology was discussed, but no satisfactory explanation was advanced, although the possibility of lymphatic spread of either infection or some breakdown product of the preparation was considered.—I am, etc.,

Sale, Cheshire. P. N. FIRTH.

SIR,—Many doctors will read with regret in your leading article (March 12, p. 788) about the possibility of a carcinogenic hazard in that most useful drug "imferon." But many will also, I think, regret the alarmist way in which the article was written, so that it hit the headlines of most of the papers next day, causing local officers of health to be inundated with calls from anxious people before some of them had even read your article. It is right that doctors should be informed of potential dangers, but it is not right that the hundreds of thousands of patients who have received imferon should be led to anticipate that they may develop a "cancer" as a result. Such a price is far too high to pay for what is at present a hypothetical possibility which has, so far as we know, not yet occurred in man. Nor is this sensationalism due to a sensational press. It is implicit in the last sentence of your article which demands its "speedy withdrawal"—a withdrawal announced in the press to-day. The carcinogenic action of cigarettes, for example, is much better authenticated, but you have never suggested their suppression.

I would suggest that a more truly scientific approach would have been to consider the implications of the animal experiments and see what steps can be taken to avoid any such hazard in man, supposing that such exists. And here a common practice in some hospitals would at once come in for criticism, that of giving a number of doses of imferon on successive days, very much more than the body could possibly absorb at once. This is bound to leave depots of iron-dextran, which might become a solid mass and cause irritation anyhow. The second is the use of the wide-bore needle which Bengers provide. In spite of the technique which they illustrate this leaves a track along which the solution seeps back and gets into non-absorbent tissues, though the hole in the skin is closed by its natural elasticity. It then spreads subcutaneously and causes widespread staining which is often painful for months and may show for over a year. Here is another way in which the iron could cause toxic or carcinogenic effects. If a smaller-bore needle is used and pressure exerted by a finger alongside it as the needle is slowly withdrawn the track is closed up immediately, and no staining or pain results so long as this pressure is kept up for a full minute afterwards. While keeping up this pressure I have, in spite of Benger's instructions, also massaged the area firmly, for from the first it seemed to me only wise to distribute the imferon in the muscle to minimize irritation and afford a greater surface for absorption. I will not say that I have never had a stain result from an injection, but fully 95% of my injections have been painless and left no mark at all.

If this technique were followed and doses not given more than once a week or so I can see no grounds in the evidence you have so far provided for banning the

use of imferon, for deposits of iron would not form, and even if in another 20 or 30 years' time a certain number of sarcomas were to develop I am sure that most of my women patients who have had imferon have benefited so much from it that they would gladly take the hypothetical risk of a sarcoma for the vast improvement in their health that it has brought. As some of them have said to me already, "I might get a cancer anyhow." "Yes," I have replied, "or get run over." This does not mean that I underrate risks, but my work on the *B.N.F.* Committee has shown me that very few drugs are without risk—as the *Formulary* itself shows—but life is an adventure, it involves a running of risks. To play all the time for safety is stagnation, and the doctor's duty is to be aware of the risks and yet be willing to run them and keep the anxiety to himself, unless it is one which he obviously ought to share with the patient or his relatives. It certainly is not to mention the risk in such a way as to put alarm or despondency in patients for perhaps the rest of their lives.—I am, etc.,

W. N. LEAK.

Winsford, Cheshire.

SIR,—After reading in my newspaper this morning that this journal had called for the "speedy withdrawal from any kind of general use in man" of "imferon" I naturally turned to the journal to see what arguments were given. It was a great surprise to find (March 12, p. 788) that these were based entirely on experiments with rodents and that you cannot even "affirm . . . let alone measure" the hazard to man despite the years the drug has been in use and the many patients who must have received it. How many cases have yet been reported of a sarcoma developing in man at the site of imferon injections? If any, are the figures significant?

If a drug has dangers it is your duty to point these out. Many valuable drugs in use to-day have serious and even fatal reactions in some patients. Often these reactions are only discovered after the drug has been in use for some time. I should not expect you to demand automatically their withdrawal from general use. After due publicity it is surely the practitioner who must assess the value against the dangers of a drug, unless the evidence of dangers in man is so great that a ban on the drug seems indicated. In the case of imferon you do not appear to have produced such evidence.

The possible carcinogenic risks of metal injections have been known for some time. Your article, which will receive publicity and possibly even a "Question in the House," is bound to cause anxiety amongst those who have received this drug. On the evidence you give this would not appear justified. Lastly, and to me my most important point, the company has stated to the press that it was surprised at your article and that it had not been previously consulted. In view of the strong feelings you obviously have on this subject it seems inconceivable to me that you should not have informed the company long ago of your views on the use of imferon. I should very much like to know what steps were taken by you to bring your views to their notice before publication.—I am, etc.,

Blaby, Leicestershire. GEOFFREY A. TAYLOR.

SIR,—I was horrified to read your leading article (*Brit. med. J.*, March 12, p. 788) about the effects of intramuscular iron injections causing sarcomata in mice. I, for one, have given a great number of these injections for anaemia of pregnancy. I understand that it is common practice to give these injections to newborn pigs, and it would be interesting to know if there have been any sarcomata reported in these. The pig is probably more closely related to man than the mouse.—I am, etc.,

Ashford, Middlesex. NIGEL G. NICHOLSON.

Mid-stream Urine from Women

SIR,—When clean urine is required from a male patient a mid-stream specimen is obtained, but when a clean specimen is required from a female patient usually a catheter is passed, as it is thought that a clean mid-stream specimen of urine cannot easily be obtained from the female. Kass[1] was able to show a close correlation between voided and catheter specimens of urine in the female with bacterial counts over 100,000 bacteria/ml. of urine. A further study of mid-stream and catheter specimens of urine in the female has been made.

To obtain a mid-stream specimen of urine the following procedure has been used: (1) The labia are parted and a swab is passed from behind the clitoris over the urethral opening and introitus to the fourchette. Three swabs soaked in an aqueous solution of "hibitane" (chlorhexidine diacetate), 1 in 2,000, are used. (2) After two minutes the same area is dried thoroughly with sterile swabs. (3) The patient washes and dries her hands. (4) She sits on the toilet seat as far backwards as possible with her legs apart and separates her labia with her fingers, as demonstrated to her by the nurse at the time of swabbing. (5) The patient passes urine, and a sterile container is placed between the patient's legs when the stream is well established.

Ante-partum and puerperal cases were selected, and patients with clinical evidence of a urinary infection were excluded. A mid-stream specimen of urine was obtained from the patient at 9 a.m. One hour later a catheter specimen of urine was taken. Within a short time the urine specimens were examined microscopically and inoculated on MacConkey and blood-agar media. Bacterial growth was reported as mild, moderate, or heavy. The urine was also tested for albumin and its *p*H measured.

In 51 female patients an attempt was made to obtain a mid-stream specimen of urine. This was successful in 40. A positive culture was obtained in six of the mid-stream specimens when the catheter specimen was sterile; five of these contaminated mid-stream specimens, however, were obtained in the first six attempts to collect such a sample. In the remaining 34 cases it was possible to obtain a mid-stream specimen of urine comparable to the catheter specimen on microscopical examination and bacterial culture. Three of these urines showed a trace of albumin, pus cells, and a positive culture; there were no abnormalities in the other 31.

In the majority of female patients it is possible to obtain a mid-stream specimen of urine comparable to that obtained by the catheter. The disadvantages of catheterization do not apply to the mid-stream technique, and it is thought that the latter method should be used in the female when a clean specimen of urine is necessary. Some female patients are unable to pass urine as required by the mid-stream technique, and one cannot relate this failure to the intelligence or personality of the patient. The mid-stream technique is contraindicated in the patient who should not exert herself, is unable to co-operate, or is in advanced labour. Despite the presence of lochia, mid-stream specimens of urine can be taken satisfactorily during the puerperium. We believe that, because of the inherent dangers of catheterization, most female patients should attempt this technique when clean urine specimens are required.

The urine was collected by four staff midwives in this experiment. After the technique was established, and excluding the first attempt of each nurse at the mid-stream technique, no contaminated mid-stream specimens were obtained. Thus the method is simple and easy to learn. In three patients pus cells and *Bact. coli* were found in both the mid-stream and catheter specimens of urine; these were puerperal cases with no pyrexia or urinary symptoms. The significance of these subclinical urinary infections is unknown, and, although the infection may disappear spontaneously and be of no significance, it could be a manifestation of a chronic urinary infection. The presence of three subclinical urinary infections in such a small series of cases requires further elucidation. A more complete study of the problem of urinary infection in pregnancy, the puerperium, and later life is being made.

In view of our findings, we believe that a case for the use of mid-stream rather than catheter specimens of urine in the female has been made.—We are, etc.,

E. C. WOOD.
J. H. M. PINKERTON.
R. M. CALMAN.

Institute of Obstetrics and Gynaecology,
Queen Charlotte's Hospital.

REFERENCE

1 Kass, E. H., *A.M.A. Arch. intern. Med.*, 1957, **100**, 709.

Spiritual Healing in Hospitals

SIR,—The National Federation of Spiritual Healers has approached a large number of hospital management committees requesting that its members be allowed to undertake "spiritual healing" of patients in hospital. We have learned, much to our concern, that 117 hospital management committees have already agreed to the Federation's request. Is it possible that this has been done in the absence of adequate information as to the status and claims of the Federation and its members and without reference to the medical advisory committees of the hospitals concerned?

We feel that attention should be drawn to the Federation's proposed "general code of conduct to be accepted by healers" (embodied in a document entitled "Spiritual Healing in Hospitals—Advice to Healers"). Although the compilers of this document are clearly very anxious to avoid arousing criticism from the medical profession, it is apparent that they have little or no real understanding of the medical ethics involved or indeed of the fact that the practice of medicine rests on a scientific basis. The following quotations are typical of the general content and condescending tone of their proposed "code of conduct":

"(4) . . . the healer can inquire of the Sister the condition of the patient and listen to any information the Sister can give. The healer should be very courteous and sympathetic and so make a friend of the Sister and earn her confidence."

"(7) If the healer is impressed to 'lay-on' hands on the patient, this should be very quietly done without any fuss. It should be remembered that this is just as effective outside the blankets, for the healing power can travel through them with ease."

"(13) If the healer feels that the medical treatment is opposed to his conviction—for example, if a joint is immobilized and the healer feels this is wrong, he should not tell the patient about it. When, however, confidence is established between the healer and the hospital staff, the healer may discuss the patient with them and suggest alternative treatment and the reason for it, in a nice way, without being assertive. The doctors have reasons for the treatment being carried out, and while the patient is in hospital the doctor is the one who is responsible. The healer can only offer suggestions."

"(15) When a patient makes a good recovery the healer should avoid taking credit for this, but share any 'credit' with the hospital."

In view of the above, we feel most strongly that members of the medical profession should very seriously consider whether or not they can enter into any kind of professional association with members of this body, and we strongly urge that those hospital management committees that have already agreed to "spiritual healers" entering their hospitals should reconsider their decision in consultation with their respective medical advisory committees.—We are, etc.,

E. R. BANNER.
I. FROST.
D. MACSORLEY.
M. C. MOSS.
R. MIDDLEFELL.
T. G. PARKER.
F. J. GALLAGHER.
M. COSGRAVE.
K. C. S. EDWARDS.

Deva Hospital,
Chester.

Clostridial Food-poisoning

SIR,—Your leading article (*Journal*, March 5, p. 711) was a timely reminder of the dangers of food-poisoning due to *Clostridium welchii*. As you note, the strains of *Cl. welchii* responsible are usually heat-resistant, and do not produce haemolysis on horse-blood agar. However, McKillop[1] showed quite clearly that haemolytic strains of *Cl. welchii* can produce food-poisoning, and, indeed, in the hospital which she investigated, it appeared that most of the contamination of cooked chicken with *Cl. welchii* occurred after the birds had been cooked and that the strains were mainly haemolytic and non-heat-resistant.

Her findings have two important implications. The first is that in an outbreak of food-poisoning a full investigation should include a search of the environment for sources of contamination of the food with any kind of *Cl. welchii*. The observation that haemolytic strains of *Cl. welchii* can give rise to food-poisoning has been made before,[2] but seems to have escaped people's attention, doubtless because the fact that non-haemolytic strains of this organism are heat-resistant allows one temptingly simple explanation to cover all cases. The second implication, as emphasized in your leading article, is that meat should be cooled rapidly after cooking and protected from liberal contamination with spore-laden dust, particularly if the meat is to be stored moist, as in a pie, and if it is to be reheated to less than a sterilizing temperature.—I am, etc.,

R. J. FALLON.

Bacteriology Department,
Western Infirmary,
Glasgow, W.1.

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1 McKillop, E. J., *J. Hyg. (Lond.)*, 1959, **57**, 31.
2 Hobbs, B. C., Smith, M. E., Oakley, C. L., Warrack, G. H., and Cruickshank, J. C., ibid., 1953, **51**, 75.

Influenza-like Illness

SIR,—During the autumn of 1959 I saw a number of patients with an illness lasting two to five days, characterized by malaise, sore throat, and muscular pains, especially across the shoulders. On examination the temperature was normal, the fauces appeared normal, but there was some tender enlargement of the cervical lymph nodes. Most patients experienced a state of

fatigue and depression for a further week or two. Several of my colleagues in north-west London reported similar findings among their own patients. On clinical grounds there seemed little doubt that this was influenza, although at this time no laboratory evidence of influenza was reported by the Public Health Laboratory Service.

In the midst of the epidemic I saw a small series of cases which initially were thought to be influenza. The course of these cases, however, was quite unlike that of influenza. Their clinical features are shown in the Table.

Case	Initial Illness	Relapse	Joints Involved	Convalescence
(1) E. K., male, aged 20	June 14: Febrile illness, headache, meningism	Aug. 18: Fever, pleuritic pain	—	Several months
(2) D. K., male, aged 18	Aug. 10: "'Flu" Aug. 18: "Pneumonia," sore throat, backache	Aug. 25: Tonic contraction limbs, fever, stiff neck, muscular pains, joint effusions Oct 17: Chest pains, myalgia, joint pains	All joints, especially knees, ankles	Four months
(3) F. K., female, aged 14	Oct. 6: "'Flu"	Oct. 9: Malaise, weakness, generalized myalgia, joint effusions	Ankles, wrists, knees	One month
(4) B. K., female, aged 52	Oct 9–19: On and off malaise, weakness, pains in the head, sweating, generalized aches and pains	Oct. 30: Acutely ill, sweating, intense myalgia, sore throat, aching joints	Ankles, wrists, fingers	Two months
(5) J. K., male, aged 52	Oct. 28: "Chill," sore throat, aching upper limbs; weakness, cough, joint effusions		Wrists, fingers	Two weeks
(6) M. N., female, aged 34	Oct. 10: "48-hour 'flu," myalgia, fever, sore throat	Oct. 19: Fever, headache, enlarged cervical lymph nodes, followed by intense myalgia and joint effusions	Wrists, fingers, knees	One month
(7) G. W., male, aged 28	Oct. 24: "48-hour 'flu" and giddy, fever, sore throat	Nov. 2: Purpuric rash legs four days, followed by slight malaise, joint effusions	Knees, wrists	Two weeks

These cases were clearly differentiated from others during the epidemic by the following features:

Joint Effusion.—This was the outstanding feature in all but Case 1. Ankles and knees were the most commonly affected joints.

Tendency to Relapse.—The initial illness was usually ill-defined, most of the patients assuming that they had "'flu." The period between the initial illness and the relapse was usually about a week, though it appears to have been two months in the first place.

Convalescence.—This was characterized by malaise, depression, and inability to concentrate. The duration of this state seems to have been directly proportional to the severity of the second phase of the illness.

Cases 1, 2, and 3 spent the greater part of their illness in hospital, the others being seen and investigated at home. *X*-rays, E.S.R., blood-counts, agglutination tests, and throat swabs were negative in all cases. In Case 1 Paul–Bunnell slide-test indicated a (?) virus infection. In Cases 2, 3, 4, 6, and 7 virus studies were undertaken, and in these no evidence of recent virus infection was found. Cases 2 and 3, however, showed evidence of past infection with adenovirus. Adenovirus causes a quite different type of illness—acute, short-lived, affecting the respiratory tract, and sometimes the conjunctivae.[1]

In every case I put "'flu" on the certificate, but what was the diagnosis?

I wish to thank Dr. C. E. D. Taylor, of the Central Public Health Laboratory, for his help in the preparation of this report, and Dr. H. Joules, Dr. K. Ball, Dr. A. O. F. Peel, and Dr. L. C. Martin for permission to quote from their records.

—I am, etc.,

London, N.W.2. S. GOLDWATER.

REFERENCE

[1] Huebner, R. J., *Mod. Med. (Minneap.)*, 1958, **3**, 1193.

High-pressure Salesmanship

SIR,—I am hoping that publication of this letter will draw the attention of our pharmaceutical industry to an added trial that has emerged from their extensive advertising campaign. Brochures and pamphlets have been getting bigger and glossier, to such an extent that they now cannot be put through the average-sized letter-box. Yesterday I received a multi-coloured brochure size 12½ in. by 9½ in., which the postman was unable to put through the letter-box. In Ealing we are fortunate enough to have an early delivery of mail, but to be roused from one's bed to take in an advertisement through the front door because it is too large to go through the letter-box is not calculated to further the aims of the advertiser.—I am, etc.,

London, W.13. R. E. W. OLIVER.

SIR,—At a recent busy surgery (nominally one hour) I was visited by representatives from five drug firms. Is this a record? Or is it, as I suspect, that this method of high-pressure salesmanship is on the increase?

Not only is this necessarily a great expense added to the N.H.S. drug bill, and a waste of skilled manpower, but it wastes our time and reduces our scanty leisure. There can be no great benefit to the consumer and taxpayer from this competition: for investigation usually reveals that, in spite of a confusing number of different names for practically identical products made by different firms, the price is the same in all cases. There might as well be a price ring. Are we so wedded to the glories of private enterprise that we dare not in an organized way protest at competition run riot for pickings from the N.H.S. drug bill?

I would like to suggest that we should demand of the drug firms that they reduce their representatives' visits to a maximum of five minutes with each practitioner per annum per firm, and I feel a corresponding curtailment of the daily avalanche of circulars should also be enforced.—I am, etc.,

Brighton, 6. R. S. SAXTON.

SIR,—Dr. Cyril Taylor's letter (*Journal*, March 5, p. 731) suggests a course which, I feel, we should all do well to follow with the object, perhaps, of bringing down the high cost of drugs.

During the last three months I have wasted a few minutes of my valuable time each day in recording the volume of literature [*sic*] received from drug houses. In 77 "postal delivery" days I received 368 communications from no fewer than 62 different firms. (I had no idea so many existed.) With commendable modesty 27 of these firms sent less than 5 communications; 26 sent between 5 and 15; 9 sent more than 15. The winner sent me 27 bits of blurb in the 77 days—about one

every third day. Two others dead-heated for second place with 25 each, and yet another limped behind with 22.

I leave it to your readers to work out the implications of these simple figures, remembering that there are over 23,000 G.P.s in the N.H.S., and that probably 99% of this advertising material goes unread into 23,000 waste-paper baskets daily. "Ill blows the wind that profits nobody."

By the way, Sir, the winner was *not* the one you first thought of.—I am, etc.,

Stirling. J. E. MORRISON.

Therapeutic Abortion

SIR,—Professor T. N. A. Jeffcoate in "Indications for Therapeutic Abortion" (February 27, p. 581) mentions the difficulty in evaluating this procedure because of lack of factual knowledge and controlled observation. He emphasizes the physical and psychological hazards of the operation, and about these there is no lack of information. He stresses that it is not enough to decide that pregnancy adversely affects disease, but that it has also to be shown that the continuance of an established pregnancy will be more harmful than its termination by surgical means. He draws attention to the fact that physicians who recommend therapeutic abortion often have little first-hand knowledge of what it entails or of how the diseased patient reacts to childbearing. "How often does a cardiologist see his patient in labour?" All this is expressed in a characteristically lucid manner.

But it is in vain that one looks for the application of these principles to a subject in which we have a special interest—that of heart disease. In Professor Jeffcoate's practice this is by far the most common indication for therapeutic abortion. For this reason he terminated 21 pregnancies from a total number of 28,000 pregnant women. This involved a major abdominal operation in virtually every case. In the National Maternity Hospital, Dublin, a city not greatly removed from Liverpool, during much the same period of time 539 cases of rheumatic heart disease were studied. The incidence of the disease was 1.5% in 36,000 pregnant women. There was no therapeutic abortion performed. Professor Jeffcoate is not likely to find a more reasonable control series.[1 2]

Our experience prompts us to make a few critical observations. The author quotes Sutherland *et al.*[3] to the effect that therapeutic abortion is indicated in about 1% of cases of heart disease. If it is reasonable to assume that the incidence of this disease in Liverpool (not given) is somewhat similar to what it is in Dublin (1.5%) he, in fact, performed it on five times that number. Such a striking discrepancy should be elucidated. Professor Jeffcoate gives reasons why abortion is rarely indicated in primigravidae with heart disease, and 19 of his 21 cases were multigravidae. He states that three small children in an unsatisfactory home might constitute an urgent indication for abortion. Yet in our series only one woman with more than two children died; she had 10 and she died from a ruptured uterus. Does this not suggest that the cases which are terminated in Liverpool are the very cases which do best in Dublin?

Though we also cannot claim exemption from personal conviction, the facts seem to warrant the following comments: (1) Professor Jeffcoate terminates pregnancy in a very high proportion of cases of heart disease. (2) The group from which he terminates most is that which experiences least difficulty if pregnancy is allowed to continue. (3) The hazards of termination, even in healthy women, are well established; it is the benefits that remain to be proved. (4) Until proof is available, good antenatal care, with avoidance of caesarean section and its synonym hysterotomy, offer pregnant women with heart disease the best chance of survival.—We are, etc.,

M. I. DRURY.
M. K. O'DRISCOLL.

National Maternity Hospital, Dublin.

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2. O'Driscoll, M. K., Barry, A. P., and Drury, M. I., ibid., 1957, **2**, 1090.
3. Sutherland, A. M., Mair, J. T., and Bruce, D. F., *Glasg. med. J.*, 1955, **36**, 411.

SIR,—Professor T. N. A. Jeffcoate is to be congratulated on performing 63 terminations of pregnancy without a fatality (February 27, p. 582). His article would have been of the greatest value if we had been given more information about these particular patients. I think, too, that his article contains some false assumptions.

(1) There is no essential relationship between the number of medical terminations and the number of confinements at any particular hospital. For example, Donnelly,[1] of Jersey City, reported the need to terminate only 8 pregnancies in over 150,000 confinements. His mortality rate was 50%—i.e., four patients died as a result of the termination. This suggests to me that his material was highly selected, and that patients went elsewhere for their terminations. It would be interesting to know how many terminations are done in Birkenhead as compared with Liverpool.

(2) We are not told how many patients were refused therapeutic abortion or what happened to these patients.

(3) Abortifacient pastes are said to be unpopular, inefficient, and fraught with danger. Barnes[2] has reported a series of 61 terminations by this method with 80% success and no serious complications. I happen to know of one firm which sells over 600 tubes of abortifacient paste each year to registered medical practitioners in this country.

(4) Psychiatric opinion is regarded as suspect except when agreeing with Professor Jeffcoate's own views, when meaningless figures are quoted.

(5) "Strict adherence to truly medical indications means that fewer therapeutic abortions will be performed." In other words, social and economic factors which we all take into consideration when advising about all other medical problems should be ignored if therapeutic abortion is in the offing. Those of us who are at "general-practitioner level" know what happens to mothers when they return home after confinement. The cardiac patient who has spent two months in hospital prior to delivery suddenly has to cope with piles of dirty nappies, the cooking, and the housework.

(6) "The present law is so strict as to control effectively criminal abortion, yet no doctor need fear its consequences if he terminates a pregnancy in good faith." The lowest minimum estimate of criminal abortions is 58,000 each year in this country, and the highest minimum estimate is 250,000 a year.[3] The mortality rate from criminal and non-criminal abortion is between 400 and 600 each year in this country. The control is not as effective as some people think. Many consultants charge no fee, or a "nominal fee," when giving an opinion about terminating pregnancy. Do they do this out of the kindness of their hearts or to protect themselves?

The person best suited to give an opinion about therapeutic abortion is the person who knows most about the patient. In most cases this person is the patient's general practitioner.—I am, etc.,

London, S.W.11. PETER DARBY.

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2. Barnes, H. H. F., *Lancet*, 1947, **2**, 825.
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Congenital Dislocation of the Hip

SIR,—I hope no G.P. who has the opportunity of examining newborn babies for orthopaedic deformities will be discouraged by the pessimistic prophecy of Messrs. E. W. Somerville and J. C. Scott (March 5, p. 724) that he may spend 40 years before finding a dislocated hip (I would prefer to express it as examining a thousand babies). Nor should he be put off by Professor Bryan McFarland's pronouncement (March 19, p. 881) that the diagnosis of these dislocations is an extremely difficult and complicated business which should be left to his betters in an orthopaedic institution at some unstated future date. The stage in human life that corresponds to the emergence of an insect from the chrysalis, though neglected by orthopaedists, paediatricians, obstetricians, and anatomists, is of vital interest and there is an infinite variety of observations to be made in it.

Through the help of certain colleagues, particularly those at a large maternity hospital, I have been enabled to examine several congenitally dislocated hips immediately after birth, while the hips still keep their intrauterine flexion and the lack of subcutaneous fat makes the palpation of the bones far easier than a few months later. This ease of palpation is important, since in that position *x*-rays give no intelligible result. These examinations were so instructive that I cannot believe anyone who has not conducted one can understand the condition. As I have been pointing out for many years,[1–4] the head of the femur is pushed out of the acetabulum before birth downwards and backwards by pressure on the knee (or on the feet in the extended knees position), and only on extension does it describe an arc on the attachment of the iliofemoral band to come to rest in the ordinarily recognized position above and behind. This shift is often mistaken for the process of dislocation itself. Hence terms like presubluxation for the early stages.

A variation on the "Ortolani click," which, of course, is caused by reducing the dislocation over the posterior lip of the acetabulum, can be easily produced by upward pressure on the great trochanter when the thigh is thus in the foetal position. This is the manœuvre which I use for reduction at any age.

As to dysplasia, the "shallow acetabulum" is undoubtedly a factor in permitting dislocation; though it may exist without this having occurred. The typical failure of development of femoral head and acetabulum, however, can be exactly reproduced in young animals by deliberate dislocation. It accordingly seems established that this kind of dysplasia is caused by the dislocation, and not the other way round.

Next to late diagnosis the commonest cause of failure in non-operative treatment is not getting the head of the femur forward into the acetabulum; unfortunately it is impossible to demonstrate the posterior position by *x*-rays, and fingers seem out of fashion as a means of investigation.—I am, etc.,

London, W.1. DENIS BROWNE.

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2 —— *Riv. Chir. Paediat.*, 1959, **1**, 3.
3 —— *Arch. Dis. Childh.*, 1955, **30**, 37.
4 —— *Aust. N.Z. J. Surg.*, 1959, **29**, 85.

Obesity in Childhood

SIR,—I read Dr. John Rendle-Short's article on obesity in childhood (*Journal*, March 5, p. 703) with dismay. For almost a decade "preludin" (phenmetrazine) has been used to lose weight and to relieve the misery that the fat endure. Weight loss has certainly been effected, but the consequences of addiction have been grave.

I have been making inquiries, and the situation has been the same in Europe and America. The consequences of the unrestricted sale of this drug are not widely known. The cycle of elevation of mood followed by depression, hallucinations, and paranoic phenomena are very common, and when restrictions upon the purchase of this disastrous drug occur the addicts' problem will remain. Will they turn to alcohol? The sales throughout the world of preludin must have been enormous.—I am, etc.,

Cardross, Dunbartonshire. PHILIP M. ELLISON.

Adenoidal Hyperplasia in a Mongol

SIR,—I was very interested in Dr. G. Parry Williams's letter (March 12, p. 799), as that week I had been confronted with an almost identical picture after inducing anaesthesia in a boy of 15 for a laparotomy.

Grossly enlarged tonsils were seen to meet in the midline at their upper poles, and lymphoid tissue from their lower poles extended medially and was contiguous with excessive lymphoid tissue in the posterior third of the tongue. The epiglottis was not seen, and a fleeting glimpse of the back of the glottis was obtained only with some difficulty. My patient, however, differed from Dr. Parry Williams's in that he was not a mongol but a fat boy with genital hypoplasia. An abdominal testis was removed at operation from the left side.

In this case instrumentation readily caused bleeding, the bulky posterior third of the tongue tended to prevent the tube coming forward to the glottis, directing it into the oesophagus. As Dr. Parry Williams points out, the possibility of associated adenoid hyperplasia contradicts nasal intubation. A difficult intubation was therefore abandoned, a Guedel's airway introduced, and anaesthesia continued via a face-mask.

It may be a comfort to an anaesthetist who suddenly meets this alarming sight on introducing a laryngoscope to know that, in spite of the apparent wall of tissue in front of him, he may well be able to maintain an airway without intubation. Thus, if his original indication for intubation had been more relative than absolute, this luxury could be forgone and anaesthesia could be continued with little more inconvenience than a pair of tired hands.—I am, etc.,

G. H. RYDER.

Upminster, Essex.

The Gas Man Cometh

SIR,—Dr. J. T. Crowley in his letter "The Gas Man Cometh" (March 12, p. 805) draws attention to the uselessness of the diploma in anaesthesia. Although the standards set for this examination are extremely low, it could and should be made meaningful and worth while. At present its status illustrates the unsatisfactory state of affairs concerning specialist examinations and higher degrees.

The diploma in anaesthesia should be awarded for experience, practical skill, and technical ability in the specialty. None of these attributes are taken into account in the present qualification for the diploma or the fellowship. The most important factors in becoming a fellow of the faculty are adequate financial resources for full-time study, and a mind capable of retaining advanced and often useless information in the fields of anatomy, pathology, physiology, pharmacology, medicine, and surgery. The important question of whether or not the aspirant can give a decent anaesthetic is left to chance. The fellowship should be left in its present state as being indicative of an encyclopaedic mind, while

the diploma should be awarded for the candidate's performance in the theatre over a long period by a number of surgeons and anaesthetists of merit—for only those for whom he has worked are in a position to judge his *practical* worth.

It is interesting to note that the fellowship in surgery is losing esteem as the diploma in anaesthesia has already done, for one cannot be certain that an F.R.C.S. is capable of practising good surgery. For all its complexity, the existing sorely strained examination system is such that many thoroughly competent and desirable specialists are repeatedly "referred," whilst others pass who shouldn't. The examination often bears little relevance to what will be required of those who pass. The reason for this is presumably due to the very large number of candidates, but this in turn is partly due to the entirely false state of affairs that has built up in these specialties.

Provincial hospitals are often undeservedly recognized as trainee establishments. Indeed most hospitals in the N.H.S. would cease to function were it not for the encouragement of many young hopefuls into believing that there is room for them at the top of the tree. Most of these trainees are destined never to become consultants and will eventually abandon their specialty. This system, which ostensibly produces better consultants by providing a larger number of aspirants to choose from, in fact results in large numbers of patients being in inexperienced hands at critical times. It ensures ever-increasing herds of candidates for specialist qualifications, which they must obtain to stay in the specialty of their choice without being perpetual nomads. It keeps the College coffers full, and it provides an uneasy, cheap solution to the sketchy staffing of provincial hospitals.

Training for consultantship should be restricted to teaching centres, and the appointment of permanent subconsultant grades should be encouraged in provincial hospitals. In this way patients would fare better on the whole than they do now, and a degree of sanity would return to the jeopardized higher specialist examinations by reducing the number of entries. Unfortunately such changes are unlikely to occur, because existing consultants would see in them a threat to their own status.

As for being the butt of surgical temper and humour, one must remember that the "gas man" in turn often has his critical ideas about the surgeon, but, being by nature an altogether calmer and more balanced individual, he keeps his thoughts to himself!—I am, etc.,

Worthing, Sussex. J. M. CLARK.

SIR,—With regard to the letter from Dr. T. J. Crowley (March 12, p. 805), conditions may of course be different in New Zealand from what they are in England, but I don't think I have ever found myself in such violent disagreement with any letter in the *B.M.J.* as I do with the last paragraph of Dr. Crowley's letter.

I did over 20 years as part-time anaesthetist and seven years, before I retired, as whole-time. I got my appointment largely through being the only D.A. within range. Also in this country the Ministry has kept its promise of treating anaesthetists as on a par with any other specialist. May I also say that I have always found surgeons very pleasant colleagues indeed?—I am, etc.,

Richmond, Yorks. R. K. ROBERTSON.

SIR,—Dr. T. J. Crowley's letter (March 12, p. 805) is worthy of serious consideration by all anaesthetists, apart from its humorous side, although I am afraid that our surgical colleagues may feel irritated by its candour.

It is undoubted that the surgeon expects to set the emotional tone of the theatre, and that if he laughs all must laugh, and if he cries all must weep. I have seen the surgeon throw a tray of instruments on the floor in a moment of pique—this was only greeted by the theatre staff as an amusing incident. Let the anaesthetist speak a little sharply to a theatre nurse and a major crisis is precipitated.

I have to "do" for some seven surgeons: the young ones are far the most appreciative and understanding, and I would like to make this point in my letter. To avoid being the target for surgical temper, I hope you will allow me to subscribe myself,

"MOTHER OF SEVEN."

Live Polio Vaccine

SIR,—The Minister of Health has revealed in a written reply to a question in Parliament that the Medical Research Council "will shortly carry out small-scale trials of Sabin oral poliomyelitis vaccines in selected areas." It is indeed remarkable that these trials, which represent a complete breakaway from the medical traditions of this country, are to be carried out without prior information to or consultation with the medical profession—particularly in view of the fact that many of us regard these vaccines as potentially dangerous. The short annotation on the subject (*Journal*, February 27, p. 628) is hardly calculated to allay our fears and, being anonymous, leaves us in ignorance of from whom we could obtain more details.

Which types of virus vaccines are to be used, or are all three types to be given: and if so, will they be given simultaneously or in sequence? What is to be the timing relationship with the other immunization procedures which eight-months-old children need? How are we to avoid spread from the recipients to persons who are not yet immune and have not offered to take part in the trials but who will, as contacts, be compelled by circumstances to take part? Are we to be given adequate warning of the intended trials—geography and timing—so that we can take measures to protect—with Salk vaccine—all those whom it is so important not to infect with such viruses—e.g., the cortisone-treated, those receiving irritant injections, the recently tonsillectomized, and the pregnant?

Finally, is the opening sentence of the annotation, "The evidence is mounting that oral poliomyelitis vaccine may give a stronger and more lasting immunity than vaccines of the Salk type," really warranted? In the Singapore experiment,[1] which is quoted, immunity against only one type of virus was attempted, and it was by no means 100% successful. In South America, I understand, competition with other viruses is believed to have reduced the efficacy of the oral vaccines; while in the Belgian Congo the outbreaks of paralytic poliomyelitis in native communities round Stanleyville, where oral vaccines were used,[2] suggests to me (*Journal*, September 6, 1958, p. 638) a real risk for neighbouring communities.

But even before one debates the safety or danger of oral vaccines, surely the profession must first consider the ethical principles involved in the use of live vaccines at all. Compulsory vaccination without consent plays no part in the control of infectious disease in this country and we are all punctilious in obtaining permission for each specific immunization to be used. With oral vaccination, leading inevitably to the infection of contacts, direct and indirect, known and unknown, healthy and debilitated, immunes and susceptibles alike, this important principle is automatically abandoned. This sort of mass compulsory vaccination without consent may be all right in Russia, where its advocates quote that it has been practised on six million people, but is it really compatible with the principles of

medicine in this and other "developed" countries? The main use for oral vaccines, it has always been stressed, is in the "under-developed" countries where the financial and practical difficulties of administering Salk vaccine are considerable, and where the already high incidence of natural immunity reduces their risk.

Is it unreasonable to ask that the Medical Research Council refrain from adding to the poliomyelitis viruses in our environment at least until our Salk vaccination programme is complete? The interval will give us time to consider the moral and ethical problems at stake and to hear both the Council's reasons for wanting to make these trials and the results of the extensive Russian trials already under intensive study.—I am, etc.,

MARGARET AGERHOLM.

Nuffield Department of Orthopaedic Surgery, Oxford.

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Polio Risk to Europeans in the Tropics

SIR,—The letter in your issue of February 20 (p. 570) from Professor Harold Scarborough in Nigeria prompts me to write stressing the necessity for efficient inoculation against poliomyelitis for all young Europeans visiting Asia as well as Africa.

A colleague and I have recently had the distress of seeing two very near relatives infected severely with poliomyelitis whilst in different areas in the Middle East. My own son was infected during a few hours' stay in Singapore with a paralytic type 1 strain, developed severe paralysis when in an isolated part of Queensland, Australia (after the usual incubation period), and was flown 2,000 miles to Melbourne to a respirator and expert supervision. In his case he had received the British-made inactivated vaccine in this country before he went abroad. As it is now known that the Salk type of vaccine available until recently has not provided sufficient cover in all cases, I am prompted to write this letter to emphasize the necessity for efficient protection.

Your issue of February 13 (p. 490) contains an annotation in which it is stated that recent issues of inactivated vaccine are of higher potency against paralytic type 1. This may be adequate or it may not. I do think that, if I had to face this problem again, I should consider seriously the use of Sabin type 2 attenuated vaccine, of which the efficacy was proved by Professor J. H. Hale and his colleagues[1] in the Singapore epidemic last year. This type of vaccine has been used extensively abroad, but customary British caution may have been overdone in its adoption for use here. Under conditions existing in tropical centres, Europeans face a more acute and serious risk.—I am, etc.,

Sunderland. R. E. JOWETT.

REFERENCE

[1] Hale, J. H., Doraisingham, M., Kanagaratnam, K., Leong, K. W., and Monteiro, E. S., *Brit. med. J.*, 1959, **1**, 1541.

Heroin in Coronary Thrombosis

SIR,—It is sometimes a matter of wonder to those responsible for treating cases of coronary thrombosis in hospital that these cases are given morphine rather than heroin as a pain-reliever when they are first seen. The result of morphine injection often is to make the patient, already inclined to sickness as a result of his attack, vomit distressingly at a time when he most needs rest.

Heroin, on the other hand, seems to lessen nausea and vomiting, and, in view of the profession's fight to keep this drug in its hands, it does seem a pity that it is not used as a routine for the severe pain of coronary thrombosis, especially as one injection is, in many cases, sufficient.—I am, etc.,

Edgware General Hospital, Middlesex. G. H. JENNINGS.

Pitfalls in Chemotherapy of Tuberculosis

SIR,—The Medical Research Council trials, in which this hospital was privileged to take part, established that in cases of pulmonary tuberculosis due to drug-sensitive strains of *Mycobacterium tuberculosis*, two of the three main anti-tuberculous drugs—i.e., streptomycin, P.A.S. (para-amino-salicylate), and isoniazid—must be given together in certain doses.

It was evident when I was in the Army Chest Centre (1952–5) that the modern chemotherapy of pulmonary tuberculosis and indeed tuberculous pleural effusion would be measured in months instead of weeks, and probably years rather than months. I therefore introduced into the Army Chest Centre the alternate-day dual-drug regime,[1] believing that in no way was I cutting across the principles of chemotherapy of tuberculosis established by the M.R.C. trials, and that by so doing there might be lessened a tendency to cumulative toxic effects of long-term daily chemotherapy. It is emphasized that the majority of the cases reported on by Large, Curry, and Harrison,[2] covering cases of partial lung resection operated on in the Army Chest Centre from October 1, 1953, until December 31, 1955, were treated on this regime. These cases are now being followed up.

As already pointed out,[3–6] this drug regime was used as first choice in the Gurkha Sanatorium, B.M.H. Kinrara, Malaya, from 1955 to 1958. Every case, except two, so treated during this period eventually became bacteriologically negative. These two cases were found to be drug resistant. We did not have available to us at that time the necessary facilities for testing drug sensitivities as a routine. Many of these Gurkha patients treated on the alternate-day drug regime have had partial lung resection carried out in the Army Chest Centre, and *all* resected material has had the most rigorous bacteriological investigations. The excellent results to date more than support the preliminary report on this work.[7] Such an alternate-day drug regime, after a period of initial daily therapy, must at least be accepted as good treatment.

If Drs. G. Poole and P. Stradling (January 16, p. 161) consider that streptomycin and isoniazid should be used exclusively in long-term chemotherapy, presumably after initial daily triple therapy and assessment of drug sensitivity, then surely they would be well advised to use the alternate-day drug regime after daily chemotherapy lasting for, say, three, six, or more months after a patient has become bacteriologically negative. Their patients would be able to give themselves streptomycin, particularly when prescribed in cartridge form using the "viule" type syringe, as is our routine in the Army Chest Centre. Furthermore, surely our results of the alternate-day drug regime warrant its routine use in the over-forties. This would appear more reasonable than the risk of intermittent chemotherapy for at least 90

days by prescribing initially daily P.A.S. with daily isoniazid together with streptomycin on alternate days in the over-forties.[8]—I am, etc.,

Connaught Hospital, Hindhead, Surrey. JOHN MACKAY-DICK.

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2. Large, S. E., Curry, R. C., and Harrison, G. K., *Brit. J. Tuberc.*, 1957, **51**, 173.
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Psychogenic Disorders in Children

SIR,—As holders of a joint paediatric-psychiatric clinic, still in an experimental stage, we would like to venture some comments on the controversial topic raised by Dr. John Apley and his co-workers in their article on psychogenic disorders in children (*Journal*, January 16, p. 191).

In the correspondence evoked by the article, doubt has been expressed as to whether it is within the paediatrician's proper sphere to deal with psychogenic components in cases referred to him. Almost every paediatrician would agree that to *treat* psychological illness is definitely beyond his scope: it is, however, very much his business to recognize it in whatever form it presents. Having done so it is surely his duty to ensure that the child and, if necessary, his parents receive treatment at the appropriate clinic. It is unfortunate that in most parts of the country child-guidance clinics have such long waiting-lists that it may be months before the child can be seen by a children's psychiatrist, and in some cases many more months before treatment can be started.

Many disorders of childhood present symptoms in both somatic and psychological fields: clearly these, as Dr. John Orme says (*Journal*, February 6, p. 425) need investigation of the whole child, including his relations to his family and his response to his environment, both at home and at school. In most cases the psychopathology of his parents is important and it is not denied that this can only be adequately assessed by a psychiatrist experienced in adult psychiatry. Children with such symptoms as vomiting, encopresis, headaches, sleep disorder, to mention but a few, may, depending on local circumstances and the preference of the family doctor, be referred originally to either the paediatrician or the children's psychiatrist. Whichever consultant sees the case first often wishes for the opinion of the other.

During the past six months we have held a weekly joint clinic at which both paediatrician and psychiatrist, with the help of the educational psychologist and psychiatric social worker attached to the child-guidance clinic, carry out a full investigation of the child and his circumstances. The clinic, which is a regional hospital board service, is actually held in the child-guidance clinic premises, where there are adequate facilities for this kind of approach to a case. This full investigation in one place is time-saving for all concerned, and it seems, so far, to be appreciated by parents and family doctors. This is especially so in a region where parents with young children have to make awkward journeys and travel long distances to get specialist advice.

We have found that some problems investigated in this way can be dealt with in their early stages, before they have become very serious, as so often happens when a child has to wait for an appointment at a child-guidance clinic. In addition, cases which for one reason or another are not suitable for treatment at a children's psychiatric clinic can be "weeded out" at once and thus do not go to swell the already overburdened waiting-list.

Such collaboration and exchanges of opinion between children's physician and children's psychiatrist can be done by post and the appointments system, but more is learnt, and faster, by the investigation and discussion of actual cases than by the writing and receiving of letters. From the paediatrician's point of view, learning about the psychopathology of children and their parents is the principal object of the joint clinic. For the children's psychiatrist the opportunity to keep in close touch with general medicine is very welcome. Most important is that, from the patient's point of view, much travelling and general upheaval is avoided.

Lastly, however psychosomatically minded general practitioners may be (Dr. Stanley Ellison, *Journal*, February 6, p. 424), it is still a fact that children are referred in large numbers to children's physicians on account of symptoms which have wide diagnostic possibilities. Paediatricians are getting used to hearing the bell tolled, but collaboration with child-psychiatrists is not, as might be supposed, a panic measure to arrest departmental atrophy, but rather an attempt to deal more effectively with the work that is heaped upon them.—We are, etc.,

EDITH M. BOOTH.
Royal Buckinghamshire Hospital, Aylesbury. DERMOD MACCARTHY.

Corticosteroids in Ophthalmology

SIR,—Mr. A. C. Shuttleworth (*Brit. med. J.*, February 13, p. 501) is indeed fortunate in obtaining his hypopyon ulcer cases before they had already been given the wonderful combination which he assumes cured them (or he would surely have mentioned it). Three recent cases of mine had had this treatment, and progressed to having hypopyon while on it before coming under my care. After stopping this and using orthodox treatment (excluding carbolization on tissues already very badly damaged) they steadily improved. Why should this be so? Where cortisone is given early, even with antibiotic, deep spread of infection occurs; whereas given late, after the infection is overcome, by which time antibiotic should not be necessary, it helps resolve the inflammatory debris. I use cortisone late for this purpose where necessary, but it must be over two years since I gave up using the combinations which I certainly condemn for non-expert use.

I have been taught and still hold that the inflammatory reaction is the body's local defence mechanism, and is of great importance in limiting and overcoming the infection. Cortisone suppresses this reaction. Even if the reaction is excessive it can be relieved by many methods additional to what Mr. Shuttleworth mentions, the simplest one being local heat. Personally, if instituting antibiotics, I would rather they were helped by the body's defences than give cortisone simultaneously, which may be considered as helping the spread of the organism. This is the antagonism which I have been at pains to stress, and for which the analogy was deliberately chosen, quite apart from the diagnosis problem.—I am, etc.,

London, E.4. JOHN PRIMROSE.

Photographing a Birth

SIR,—I very much regret that the *Scottish Daily Mail* should have so upset Dr. Arnold B. Cowan (March 12, p. 801) as to cause him to make "medically public" his amazement and disgust at its report about an expectant mother photographing the actual birth of her child at St. Mary Abbots Hospital, London. Dr. Cowan expresses his hope that the hospital will reflect carefully on its decision to allow the intimacy and privacy of the confinement from being turned into a "circus."

I would be interested to know the source of Dr. Cowan's information concerning decisions made by this hospital. Could it possibly be the same daily paper? May I hasten to allay Dr. Cowan's sense of disquiet and amazement? Neither the hospital authorities nor I, as the consultant in charge of this particular case, would permit such photographs being taken at any time. The patient herself had neither the desire nor intention of taking photographs of the actual birth of the child. In short, Sir, I fear Dr. Cowan puts too much credence upon what he reads in his daily paper, and would be well advised to make sure of the facts before making criticisms of this nature and in this manner. I can also scarcely credit that he would deprive any patient of medical care purely as a form of protest.—I am, etc.,

St. Mary Abbots Hospital, London, W.8. FRANK DENNY.

Massive Gastric Haemorrhage after Salicylate

SIR,—Referring to Dr. M. A. Hussain's case of massive gastric haemorrhage after salicylate (*Journal*, February 13, p. 505), an estimation of the prothrombin time would have shown if the six "disprins" (acetylsalicylic acid and calcium carbonate) a day the patient had been taking had had a significant prothrombopenic effect, and if so the administration of vitamin K_1 parenterally would have corrected this, done away with the need for operation, and the patient would still have his stomach. I am sure that this was not the case, as doses of over six grammes per day of salicylate have to be taken to produce a prolongation of the prothrombin time and even higher doses to get beyond the critical level when bleeding is liable to occur.[1]—I am, etc.,

Leeds, 8. M. DALES.

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Visual Acuity of Drivers

SIR,—Mr. D. J. K. Wilkie (March 5, p. 722) has drawn attention to the importance of ensuring that drivers are, in fact, able to reach the legal minimum visual requirement of reading a standard number plate at 25 yards. The regulations state that inability to achieve this "in good daylight" is a bar to the granting of a driving licence.

The degree of illumination in the room in which the test is undertaken may have a considerable effect on visual acuity. Fourteen drivers aged 50–65 were tested on Snellen's types indoors with an illumination of 35 lumens on the test chart and immediately afterwards out of doors in June and July, 1958, in conditions varying from cloudy to bright sunshine. One of the eyes improved in visual acuity from 6/60 to 6/12 outdoors, and 10 eyes improved at least three lines on the test chart; all 28 eyes improved at least one line. This effect is due partly to an increase of visual efficiency in high illumination, but largely to the reduction in the size of the pupil. Its importance in relation to driving at night is obvious; a driver's nocturnal vision may be worsened by this intrinsic factor as well as by reduced visibility. Perhaps the regulations should be amended to include a minimum visual standard under conditions of poor illumination.—I am, etc.,

London, W.8. L. G. NORMAN.

Smokers' Lung Cancer

SIR,—Dr. H. Leighton Kesteven suggests (*Journal*, February 13, p. 504) that the cigarette-smoker's cough is due to some irritant in the paper-smoke and not to tobacco-smoke, basing his opinion on the fact that cigarette-smokers stopped coughing when pipe-smoking was substituted instead. I have not seen any evidence to prove or disprove this theory, which has been advanced previously.

I believe I am right in saying that cigarette-tobacco used in this country is mainly flue-cured, whilst leaf for pipe-tobacco is air-cured and then the leaf allowed to die naturally. Leaf for cigars is usually air-cured and then subjected to fermentation. In America, where the incidence of lung cancer is less than in the United Kingdom, although cigarette-smoking is heavier, the method of curing leaf for cigarette-tobacco is the same as for pipe-tobacco in this country. This may be one of the factors of the lower incidence of lung cancer in America. As Dr. Kesteven's observations have been made in Australia it would be of interest to know how cigarette-tobacco is cured in Australia and whether the method is different for pipe-tobacco there.—I am, etc.,

Wimborne, Dorset. WILLIAM E. HADDEN.

African Affairs

SIR,—It is to be hoped that the B.M.A. Council will not accept Dr. J. L. McCallum's suggestion (*Journal*, January 23, p. 281). Dr. Banda was detained because people well-qualified to judge the circumstances considered that activities associated with his presence in Nyasaland constituted a threat to public order and to the safety of his fellow citizens. The fact of his being a doctor—or a member of the B.M.A.—is quite irrelevant.

It would be an unwelcome surprise, too, were the Council to agree that the detention of Dr. Banda is "much worse" than the exclusion, for racial reasons, of a law-abiding citizen from a hospital.—I am, etc.,

Adeoyo Hospital, Ibadan, West Nigeria. T. B. RANKINE.

Old St. Thomas's Hospital Operating Theatre

SIR,—Some three years ago the female operating theatre of old St. Thomas's Hospital was discovered by Mr. Raymond Russell in the roof space of the Chapter House in St. Thomas's Street. Many of your readers may not know that St. Thomas's Hospital used to be on the opposite side of the street to Guy's Hospital until it was forced to move by the coming of the railways in 1860. In the *Guy's Hospital Reports* (1957, **106**, 133)

Mr. Raymond Russell has written a full account of this early 19th-century operating theatre.

As the theatre is of considerable historical interest and importance a committee has been formed to restore it to its former state. Much research is necessary and we feel that some of your readers may be able to help us in two ways. (1) If they know of any drawings, paintings, photographs, etc., of the old St. Thomas's Female operating theatre or of any other information about it. (2) If they know of any early 19th-century theatre equipment or furniture such as side-tables, wash-bowls, hanging-lamps, chairs, or seats, etc. It is probable that there is much material of this sort tucked away in hospitals around the country and they could prove invaluable in the restoration.—We are, etc.,

St. Thomas's Hospital, London, S.E.1. NORMAN BARRETT.

Guy's Hospital, London, S.E.1. RUSSELL BROCK.

POINTS FROM LETTERS

Diets for Lowering Serum Lipids

Surgeon Captain T. L. CLEAVE, R.N. (Lee-on-Solent), writes: May I be permitted to point out that none of the books and other references quoted by Professor J. F. Brock (March 5, p. 724) on the use of unsaturated fats in the home, for the regulation of blood cholesterol, appears to pay the slightest attention to natural laws. In a small work,[1] and later in an extended correspondence in the *Lancet*,[2] an effort was made by the writer of this letter to demonstrate the fundamental fallacy of supposing that the long-term prevention of coronary disease could ever lie in substituting fats that the human organism is not evolved to consume for those that it is evolved to consume.

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1 T. L. Cleave, *Fat Consumption and Coronary Disease: An Evolutionary Answer to This Problem*. 1957. John Wright, Bristol.
2 *Lancet*, 1959, 1, 365 and 632.

"Do-it-Yourself" Enuresis Alarm

Mr. W. H. STANTON (chief technician (electronics), department of psychological medicine, Royal Victoria Infirmary, Newcastle upon Tyne) writes: The letter from Dr. J. B. Metcalfe (December 26, p. 1488) has been brought to my notice. While holding no brief for, indeed condemning, manufacturers who inflate the prices of electro-medical apparatus, I would like to criticize the assumptions made in this letter. The circuit given is extremely crude, and, while it may work to Dr. Metcalfe's satisfaction, it would not satisfy my criteria. It is necessary to include a sensitive relay in the circuit in order to reduce the operating current so that the alarm will be set off as soon as possible after urination commences. This relay also can perform the operation of disconnecting the metal electrodes from the highly inductive bell circuit, failure to do which would result in the patient receiving electric shocks under certain conditions.

Dilatation and Curettage

Dr. B. P. BHATTACHARYA (The Georgetown Hospital, British Guiana) writes: I entirely agree with Mr. W. C. Spackman (October 24, 1959, p. 827) that quite a fair number of dilatations and curettages are performed in every gynaecological unit, some of which could be argued to be not only unnecessary but injurious. I can recall at least two young women with rupture of the internal os uteri following dilatation and curettage tearing the main uterine vessels, with severe, persistent, and intractable haemorrhage necessitating hysterectomy in the end. In British Guiana, "D. and C." to the average working-class women of low literacy is known as "cleaning out," the necessity of which is felt by them from time to time. Naturally the incidence of pelvic inflammatory diseases is fantastically high.

Obituary

J. C. BROOM, O.B.E., M.D.

Dr. J. C. Broom, a senior research worker in the Wellcome Laboratories of Tropical Medicine, died at his home in Parliament Hill Fields on March 16 after a short illness.

John Constable Broom, a son of the manse, was born at Leuchars, Fife, on September 28, 1902. He studied medicine at the University of St. Andrews, and graduated M.B., Ch.B. in 1924, later proceeding to the M.D. in 1929, when he was awarded the Rutherford medal. After a series of resident appointments in England and Scotland he joined the staff of the Wellcome Bureau of Scientific Research (as it was then called) in 1928, and remained with this unit—now known as the Wellcome Laboratories of Tropical Medicine—until his death. In the early years of this appointment he worked with the late Major H. C. Brown, and was closely associated with him in devising "Brown's Opacity Tubes" which were for long used in the standardization of vaccines. With Brown he also worked on the electrophoresis of trypanosomes from artificially infected mice, and showed that relapses were usually associated with a change in the electric potential of the trypanosomes. During the war years he was in charge of the yellow-fever immunization centre in the Wellcome Building, when he inoculated many famous people. For his services in this capacity he was awarded the O.B.E.

In his later years his main interest was the study of leptospirosis, a subject in which he became an international authority. He organized numerous surveys designed to ascertain the prevalence of infection in wild rodents. The first of these, in collaboration with Dr. (now Professor) Robert Kirk, was on sera from rats in the Sudan. He then investigated the incidence of infection in the wild rats of London, using both isolation and serological techniques. This was followed by a very comprehensive survey of the occurrence of the disease in the rats of Wales, and finally of its prevalence in rats and hedgehogs in Scotland. In the last of these surveys two types of leptospire were isolated which had not previously been described in this country. Apart from these, *Leptospira icterohaemorrhagiae* was the only type found in Britain. His field of operations was not confined to this country. He made contact with those interested in the subject in all parts of the world, and to his laboratory—which was nominated an official Leptospira Reference Laboratory—there came a constant stream of specimens, in particular from Malaya and from Australia. To his laboratory, too, there came many visitors who were assured of a courteous welcome, and with whom he was happy to discuss common interests and problems, freely giving advice based on his wide, indeed unique, experience of the subject. Much of his work is embodied in the book *Leptospirosis in Man and Animals*, published in 1958 in association with Dr. J. M. Alston. He was one of the "founder members" of the Leptospira Subcommittee of the International Committee on Bacteriological Nomenclature and had been its secretary since it was inaugurated. He was the author, or joint author, of some 44 scientific papers, and his Milroy lectures given before the Royal College of Physicians on the subject of "Leptospirosis in Man and Animals" were published in this journal in 1951.

A keen mathematician, he interested himself in the statistical aspects and control of laboratory experiments. He had a sound grasp of finance, and for 13 years gave valued service as treasurer of the Royal Society of Tropical Medicine and Hygiene.

Broom was of a retiring and rather shy disposition, but, once the barriers were broken down, was a warm and constant friend. He was not interested in field sports or games and occupied his spare time in walking or reading. His principal hobby was his work, and in this he found the most congenial outlet for his energy. His sudden death came as a great shock to all his friends and colleagues, by whom he was held in affectionate respect.

Dr. Broom is survived by his widow.—J. S. K. B.

J. R. BULMAN, M.B., Ch.B.

Dr. J. R. Bulman, one of Hereford's best-known physicians, died in the General Hospital there on February 17 at the age of 74.

John Roderick Bulman was born in Kelso on July 16, 1885. Graduating M.B., Ch.B. at Edinburgh University in 1913, he held an appointment as house-physician in the Edinburgh Royal Infirmary before joining the R.A.M.C., in which he served with distinction during the first world war. After demobilization he joined the late Dr. F. H. Thompson in partnership in Hereford and spent the whole of his professional life there. He built up a large and successful practice and was also honorary physician to the Hereford General Hospital, being on the staff for 23 years. He took a leading part in the medical affairs of the district, and for many years he was secretary of the Hereford Division of the B.M.A., of which he later became chairman, and of the Worcestershire and Herefordshire Branch, of which he was president in 1934–5. After the second world war he was the leading figure in the revival of the Hereford Medical Society, whose members made him a presentation on the occasion of the society's centenary a year ago. He had many interests outside his practice, and for many years was prominent in the life of the city and a member of the city council. A Freemason and a leading member of the Hereford Burns Club, he was an excellent after-dinner speaker.

A colleague writes: One of the kindest of men, Dr. Bulman was a typical example of the old-time family doctor. He was in poor health for a number of years prior to his death and was forced to retire from practice three years ago, to the regret of his many patients. During the last two years his health was so poor that he was confined to his house for the greater part of each year. Though in constant discomfort, he was brave and cheerful to the end and was always happy to see his friends.

Dr. Bulman leaves a widow, a daughter, and four sons, one of whom is a doctor in Australia.

P. W. G. TASKER, M.D.

Dr. P. W. G. Tasker, who was on the staff of the Institute for Medical Research, Kuala Lumpur, Malaya, died suddenly in Kuala Lumpur on March 2. He was 35 years of age.

Peter William Gedge Tasker was born in Malaya on May 19, 1924, the son of a bank manager. From Haileybury School he went on to the London Hospital, graduating M.B., B.S. in 1947 and proceeding M.D. ten years later with a thesis entitled "Nutritional and Pregnancy Megaloblastic Anaemia—Some Aspects of the Disease Encountered in Malaya." Soon after qualification Dr. Tasker returned to his birthplace, Kuala Lumpur, to join a group of British general practitioners. In the course of his practice he became interested in the anaemias so common among the labourers on rubber estates. At first he collaborated with workers in the Institute for Medical Research in the investigation of these anaemias, and so interested did he become that he abandoned a lucrative career in general practice and joined the Institute staff at the end of 1952. He was able to confirm that iron deficiency was the main cause of these anaemias.

In 1956 he received a grant from Colonial Development and Welfare funds and spent study-leave at Harwell and at the isotope department of St. Bartholomew's Hospital, studying radioactive tracer techniques. He returned to the Institute and set up a laboratory to study anaemias, being probably the first person to use radioactive tracer techniques for this purpose in South-East Asia. He used radioactive iron to study the absorption and turnover of iron in anaemic patients; radioactive chromium to label erythrocytes in order to determine blood-loss from hookworm infestation (patients were found to lose up to 3 oz. of blood per day in this way); and radioactive cobalt to label vitamin B_{12} in treatment studies. He wrote a valuable series of papers on the nutritional anaemias and anaemias of pregnancy in Malaya, but because of the inevitable time-lag in setting up an isotope laboratory from scratch his untimely death must leave much valuable work incomplete and unpublished.

A first-rate and dedicated research worker, Peter Tasker was a keen amateur pilot and took part in "pay-drops" to isolated rubber-estates and mines during the terrorist emergency in Malaya. He leaves a wife and a young family.—C. E. G. S.

J. M. TAYLOR, M.R.C.S., L.R.C.P.

Dr. J. M. Taylor, who practised as a psycho-analyst in London, and recently worked as a part-time consultant psychiatrist for the London County Council, supervising work done at certain schools for maladjusted children, died on February 15 after a long cardiac illness. He was 60 years of age.

Both James Maberley Taylor and his brother John Lupton became doctors like their father, John W. Taylor, who was a well-known gynaecologist in Birmingham. James qualified from St. Bartholomew's Hospital in 1929 and became a general practitioner in the Waterloo Bridge district and then in a country area near Cambridge. He was very fond of general practice, but all the time he had a wish to become a psycho-analyst, and managed to qualify as an analyst while working in general practice. Before making up his mind to be a doctor he had started on a career which would have made proper use of his profound knowledge of English and French literature, and during this period he worked first at Hudson's, the Birmingham booksellers, and then for some time at Blackwells, Oxford.

In the first world war he served with the French Ambulance Unit, which he joined at the age of 16, and at this early age he had close contact with death and suffering. He was proud to have acquired familiarity with the French vernacular in the front line.

Working as a psycho-analyst—he was an associate member of the British Psycho-Analytical Society—he steadily built up his experience, being particularly interested in the special requirements of patients who had been somewhat deprived emotionally in childhood. This experience came to fruition particularly in his work with maladjusted boys at the L.C.C. special schools. Here the combination of his skill as an extremely shrewd clinician and a special ability to tolerate aggression and hostility without losing sight of the potential good qualities was of great help to the boys and to the other members of the school staff. During the last decade of his life his work was sometimes interfered with by his increasing physical distress, and towards the end when he had to give up patients that he knew were still dependent on him he suffered intense grief.

He was very much loved by his friends, who always felt the warmth of his personality when they were with him. With his death there comes to an end an exceptionally rich interweaving of cultural attainments and clinical experience.

Dr. Taylor leaves a widow, Dr. Rosalie Taylor, and his

friends offer their deep sympathy to her and to John Cranes Taylor, the son of his first marriage.

J. P. H. writes: Others will have known James Taylor longer than I and seen more of his work as general practitioner and psychiatrist. I saw the illnesses which gnawed at him for so many years and would have consumed a lesser man long since. Thus it is his determination and courage that will chiefly stick in my memory—the qualities that kept him in active practice as a psychiatrist until two weeks before his death. The same qualities showed themselves in his work: it was the difficult cases that he really enjoyed; he would have been impatient with easy problems and seemed to have none. What was remarkable was the dominance of these qualities in a man who was exceedingly considerate and sensitive, who loved listening to the organ music of Bach and reading the essays of Montaigne. For the Thames, too, he had a particular love, and for his old Pontiac car, that powerful monster to drive which became in his last days an exquisite and forbidden pleasure. If determination could have defeated his illness, he would have lived—and worked—much longer.

H. E. W. H. writes: I first met James Taylor when I was a junior psycho-analyst and he one of many years' standing. He went out of his way to put me at my ease, and I was struck with his friendliness and hospitality. At that time he was already physically ill; he usually carried a stick, and often had a rug over his arm, as he felt the cold acutely. I came to know him as a gifted and unusual man. Not only was he familiar with the French classics, but he had extensive knowledge of the moderns, in particular Colette, whom he greatly admired. In English literature he preferred the poets, and he had a deep knowledge of the Bible. He had much to offer, but his illness and retiring nature prevented him from becoming widely known in his latter days among the psycho-analysts. His many interests were subordinated to a basic interest in his analytical work and his work with maladjusted children for the L.C.C. In the latter he was able to make a unique contribution because of the especial combination of clinical experience, shrewdness, and diagnostic skill which he possessed.

His second wife, Dr. Rosalie Taylor, supported him through his long periods of illness, realizing that, like many doctors, he disliked being fussed. Our sympathy goes out to her in her great loss.

BARBARA G. R. CRAWFORD, M.B.E., M.B., Ch.B.

Dr. Barbara Crawford (née Rutherford), who died on December 29, 1958, practised for some twenty years in Leamington Spa.

Barbara Grace Rutherford was born at Rothesay, Isle of Bute, on March 2, 1890, daughter of the Rev. J. Rutherford. Educated privately, she entered Glasgow University to study medicine, graduating M.B., Ch.B. in 1911. Her brother William and sister Margaret also graduated in medicine at Glasgow University. After assistantships in general practice she held resident appointments in Shirley Warren Infirmary, Southampton, and the Leicester Isolation Hospital and Sanatorium. From 1917 to 1920 she was chief medical officer to a Government explosives factory in Chester. She became an expert on T.N.T. poisoning, contributing an article on the subject to this journal in 1918, and for this work and her other services during the first world war she was appointed M.B.E.

In 1915 Dr. Rutherford married Mr. George Robert Crawford. Twelve years later, on her husband's retirement from farming, they settled in Leamington Spa, where she built up a private practice and worked for over twenty years. In spite of much ill-health in later years she continued to do some medical work until shortly before her death.

An active member of the B.M.A., she was chairman of the Warwick and Leamington Division from 1939–40. She also took a keen interest in the work of the Leamington Medical Society, the Leamington Marriage Guidance Council, and in a wide variety of matters of scientific and public interest. During the early years of her professional career she was among the first to give advice on birth control both in clinics and in her own practice, and she had a paper on the subject published in 1922. It was a great satisfaction to her in later life to see the views she had supported in her youth become widely accepted.

Dr. Crawford's husband died in 1952, and she is survived by a daughter, who is also medically qualified, and two sons.

S. F. ALLISON, M.B., Ch.B., D.P.H.

Dr. Stuart F. Allison, formerly medical officer of health of Warrington and later in practice at Hindley, Lancashire, died at his home there on January 31 at the age of 61 years.

Stuart Frew Allison was born on July 18, 1898, at Greenock. Having graduated M.B., Ch.B. at Edinburgh University in 1923, he obtained the D.P.H. at Cambridge in 1924 and also the Certificate of the London School of Tropical Medicine. After holding resident appointments at Edinburgh Royal Infirmary he became senior resident medical officer at Bristol Children's Hospital and senior resident medical officer at Bristol Infectious Diseases Hospital and Sanatorium. He then entered private practice in Bristol for a short time, but was later appointed assistant medical officer to the City of Bristol in 1930. Two years later he moved to St. Helens, Lancashire, as deputy medical officer of health and deputy medical superintendent of the corporation hospitals, and in 1934 he became medical officer of health and superintendent of the Isolation Hospital at Lowestoft. From 1937 to 1949 he was medical officer of health of Warrington and medical superintendent of the corporation hospitals. In his early years there he was closely concerned with the work of expanding and modernizing the Warrington General Hospital. His interest in the expansion of hospitals found further scope during the war years, when he was engaged with the building, equipment, and administration of an emergency hospital of 240 beds, together with the general administration of the four municipal hospitals. It is for his activities in the hospital sphere and in the developments which were carried out during his period of office that he will be most remembered in Warrington.

He had a wide interest in the public-health service, but his great love was for clinical medicine and hospital administration, in both of which he excelled. Soon after the inception of the National Health Service he moved to the post of principal administrative medical officer to the Dumfries and Galloway hospital board. After two years he broke his long connexion with hospital administration to return to private practice in South Lancashire, taking over a large industrial practice at Hindley, where he remained until his death.

At all times Dr. Allison would spare no efforts to secure the best medical attention for anyone in need of it. He always placed the personal side of the service first, and administrative processes were never allowed to interfere with meeting the needs of patients under his care. He is survived by a widow and two sons, to whom deep sympathy is extended by his many patients and friends.

Dr. T. B. S. DICK writes: During the last eight years, while Stuart Allison was in practice at Hindley, it was my good fortune to meet him on many occasions. Although he came to general practice rather late in life he was ideally suited to it. A shrewd and kindly man with a great sense of humour, he loved people. His humour was never unkind, but the vagaries of human behaviour were an unfailing source of amusement to him, and his comments on life and people were a delight to his friends. Half an hour of talk over a cup of tea at his home with him and his wife was enough to lighten the gloomiest of winter evenings. During his last long and painful illness one marvelled that his courage and humour never failed. By his many patients and friends he will be sadly missed.

H. G. HANAN, M.B., Ch.B.

Dr. H. G. Hanan, who was in practice at Mevagissey, Cornwall, died at his home on February 1, aged 54.

Hugh Grant Hanan was born at Bath on May 11, 1905, and was educated at Cork Grammar School and Edinburgh University, where he graduated in 1928. After holding house appointments at the Royal Infirmary and the Deaconess Hospital, Edinburgh, he settled in general practice at Northallerton, acting also as medical officer of health to the Northallerton urban district council. From his student days he had never enjoyed perfect health, and in 1943 he moved to the more temperate climate of Mevagissey, where he was actively engaged in general practice up until eighteen months before his death.

During his university days he was a keen rugby player and a swimming blue. He was always keen on sailing, being a member of the Royal Munster Yacht Club, and Mevagissey was ideally situated for him to enjoy this pursuit to the utmost. Having all the qualities of the traditional family doctor, he was loved by his patients, whom he looked after with scrupulous care, and he made frequent long journeys to visit them in hospital, where he was always welcomed by the hospital staff. He bore his terminal illness over the last eighteen months with great fortitude and courage.

He leaves a widow, daughter, and son, to whom we offer our deep sympathy.

C. K. McDONALD, M.D., D.P.H.

Dr. C. K. McDonald, bacteriologist to Lewisham Hospital, died suddenly on February 6 at the age of 47.

Charles Knight McDonald was the elder son of Mr. and Mrs. Alexander McDonald, of Perth. Having graduated in medicine at the University of Edinburgh in 1936, he worked for a time as assistant bacteriologist and clinical tutor at Edinburgh Royal Infirmary before being appointed county bacteriologist for Ayrshire. From 1945 to 1947 he served with a Friends' Ambulance Unit in China, where he underwent many hardships. In 1948, after a period as pathologist at the mental hospitals group laboratory at West Park Hospital, he was appointed pathologist at Lewisham group laboratory, where he was in charge of the bacteriological department. He proceeded to the M.D. of Edinburgh in 1949.

E. N. A. writes: during his period at Lewisham Dr. McDonald showed a very wide interest in the development of the hospital as a whole, and apart from his bacteriological work, in which he maintained a scrupulously high standard, he was actively concerned in the rebuilding of the hospital, particularly in the development of central sterilization facilities. An individual of very strong character and with decided views on many matters, he was not afraid to put his opinions forward, and fought hard for them whatever the majority on the other side: his absolute honesty of purpose made his opponents appreciate his views, even if they disagreed with them.

His main personal attribute was one of kindness and sympathy. His relations with all his colleagues were most cordial, and the junior staff found him an approachable and sympathetic friend. Outside the hospital he was active in many fields: he was on the committee of the local Labour party, a governor of the Lewisham Prendergast School, manager of several primary schools, chairman of the Euthanasia Society, and a member of council of the Ethical Union. An individualist, he did not conform to any expected pattern (his cars were frequently a surprise to his colleagues). He was interested in music—classical and jazz—modern art, and the theatre, Shakespeare in particular, and he used often to visit Stratford. His death leaves a gap in many places, and he will always be remembered with affection by his colleagues. Our sympathy goes out to his mother and to his brother and sister, both of whom are members of the medical profession.

NORMAN BRIGGS, C.I.E., M.R.C.S., D.P.H.

Colonel Norman Briggs, who was formerly in the Indian Medical Service, died suddenly at Eastbourne on March 3 aged 68.

Norman Briggs was born on November 12, 1891, and was educated at Hymer's College, Hull, the University of Leeds, and University College Hospital. He qualified in 1914 and took a temporary commission in the R.A.M.C. on the outbreak of the first world war, during which he served in France and Belgium and later in the Persian Gulf and Persia. In 1917 he obtained a regular commission in the Indian Medical Service. A few years after the war he was transferred to civil employment in the jail department of the Punjab, where he rendered excellent service in the Borstal institution in Lahore and later as superintendent of the Central Jail. In 1934 he was appointed deputy inspector-general of prisons in the Punjab. Two years later Briggs was selected for the combined post of director of health services and inspector-general of prisons in Sind. In this relatively small new province the tripartite division of medical administration into hospitals, public health, and jails—the administrative method obtaining in the older and larger provinces—was considered extravagant and unsuitable. During his period of office in Sind Colonel Briggs had plenty of opportunities to demonstrate his capacity for sound administration. Early in the second world war he was recalled for military duty in India, but returned to civil employment in 1943 as inspector-general of civil hospitals in the United Provinces. He remained in that post until 1947, when independence and partition ended the activities of the I.M.S. He was a kindly, friendly, hospitable man who was greatly liked by both senior administrators and his subordinates. Appointed C.I.E. and King's Honorary Surgeon in 1946, he became a Commander of the Order of St. John of Jerusalem in 1948. On his retirement he went to live at Heathfield in Sussex.

Colonel Briggs married Olive Margaret, daughter of H. Irving Bell, of Eastbourne, and she survives him.

Sir ROBERT HUTCHISON, Bt., M.D., LL.D.

F.R.C.P., Hon.F.R.C.P.Ed.

The obituary of Sir Robert Hutchison was published in the *B.M.J.* of February 20 (p. 571).

Dr. FRANK RIGGALL writes from Prairie Grove, Arkansas: Regret at Sir Robert Hutchison's passing will be world-wide. His integrity was plain. Having graduated from a trans-atlantic school in 1923, I was seeking knowledge in London in August, 1924. The hall-porter at Great Ormond Street directed me to Alexandra Ward. There, bending over a crib, fumbling in his tail pocket for a stethoscope, was a tall man. Straightening up, he told the group assembled that he did not know what was the matter with the poor child, that she had been in hospital two weeks, had been seen by two colleagues, and they could not make a diagnosis. It sounds strange, but I did not remember hearing one of my teachers make such a statement. They always knew! I learned that others in the group, like myself, would soon leave England for their respective homes, and any diagnosis could have been given us. I resolved never to be ashamed to say I did not know, provided I had made proper efforts to know. On visits to England in 1928, 1931, and 1934 I sat at Sir Robert's feet. I read everything he wrote, and valued it highly. Sir Robert is gone, but his tradition will linger long in British clinical medicine.

FRANK BARNES, LL.D., M.S., F.R.C.S.

The obituary of Mr. Frank Barnes was printed in the *British Medical Journal* of March 5 (p. 733).

Dr. D. MURRAY BLADON writes: I was extremely sorry to read of the death of my old chief, Mr. Frank Barnes, at the advanced age of 90. It is difficult to imagine "Frankie" as being 90; he always seemed to be in his prime and never

to get any older. I had the great privilege of being one of his dressers in 1923, and one of the last of his house-surgeons in 1927, a year or two before his retirement from the active honorary staff of the Birmingham General Hospital. To work with him was an education in itself, and left a lasting impression which is always with one when examining a patient or carrying out any surgical procedure. He had a supreme efficiency and complete mastery of every technique, combined with a manner of absolute calmness. He hardly ever spoke when operating and was never known to swear or show any irritation; his manner ensured absolute quietness on the part of everyone else in the theatre. He had learnt his surgery at a time when it was important to get the job done as quickly as possible to shorten the anaesthetic, and he operated at incredible speed, relying on his H.S. to place the correct instrument in his hand each time he held it out, and never having to clip a vessel a second time or having to hesitate in the application of a clamp. His list would often start with two or three "gastrics," each one of which would take exactly 55 minutes, and would include appendicectomy, partial gastrectomy, and posterior enterostomy. Five major operations was about the usual programme on two mornings a week, and Frankie would drive away at 1 p.m. as fresh as when he had started and all ready for an afternoon's consultations and a few private operations in the evening. He was one of the giants of surgery, and I doubt whether he has had many equals.

WILFRED HARRIS, M.D., F.R.C.P.

The obituary of Dr. Wilfred Harris was published in the *Journal* of March 5 (p. 732).

A. E. S. writes: I first heard of Dr. Wilfred Harris when I was Mr. C. H. Fagge's house-surgeon at Guy's after the 1914–18 war. There was a man in Lazarus Ward with trigeminal neuralgia. Several injections had failed to relieve him. "If anybody can do this patient any good," said Fagge, "it is Wilfred Harris." The patient was sent with a note to Wilfred Harris and returned relieved the same day. Wilfred Harris was a quiet, charming, and friendly man. Only last year he wrote that he was still injecting "trigeminals." Just after his 90th birthday he wrote very cheerfully.

Medical Notes in Parliament

PROCEDURE FOR FILLING PRACTICE VACANCIES

[FROM OUR PARLIAMENTARY CORRESPONDENT]

Objections to the three-tier structure in the selection of doctors to fill advertised vacancies in single-practice areas were expressed in the House of Commons on March 14. They arose from representations made by the Southampton Executive Council to the two local M.P.s—Mr. HORACE KING (Itchen, Lab.) and Mr. JOHN HOWARD (Test, Con.).

Needless Delay

Mr. KING put the case, in a half-hour debate on the motion for the adjournment. It was that the system caused needless delay, and that it appeared to call in question the ability and authority of the local executive councils. He claimed also that a recent letter which the Minister and the Medical Practices Committee had sent to local executive councils totally ignored what was said by Mr. Bevan in 1946 about how it was intended the system should work. The Medical Practices Committee claimed that it might have special knowledge of particular applicants. If that was so, it should pass on the knowledge to the executive council when the appointment was being made. The Minister's view, as quoted in the letter, was—"In the matter of selection for a vacancy the Medical Practices Committee has to give meticulous consideration to all applications." It stated of an appeal—"The Minister considered that the appellant ought to be selected on account of his experience and because his personality is not less impressive than the candidate selected by the executive council." That might be contrasted with the statement of Mr. Bevan when the Health Service Bill was in committee in June, 1946—"The Minister ought not to tell the local executive councils what grounds they should consider in making an appointment."

Executive Councils Protesting

Executive councils were protesting, in his view rightly, against what was happening to-day. They now had some 15 years' experience of administering this part of the Service. They felt that their part in making an appointment ought to be what Parliament intended it should be when the Act was passed. There still was, as late as the Cohen Report, a suggestion that the local council might be susceptible to improper influences. Both laymen and medical men on the local councils resented this. They suggested reasonable reforms: that they should make the appointment, subject to only one check, an appeal to the Medical Practices Committee; and that appeals should be restricted to those who had got on to a short list.

Mr. King cited a series of cases to support his argument, and urged that the Minister should change the current practice. Under the 1954 Regulation 10(3) he had power to deal with an appeal himself or to set up an appeal body. He should use it in a way showing more confidence in the judgment and integrity of the executive councils. He could at least adopt the common-sense attitude that if a man had not got as far as the short list drawn up by a competent selecting committee it was extremely unlikely that he was the man who should have the job; or that, if both local executive council and central Medical Practices Committee agreed, it was not unlikely that they were right. He could also urge the Medical Practices Committee to get rid of the idea of "meticulousness" in the exercise of what was meant to be a reserve power, and itself have more confidence in the executive council.

Mr. HOWARD, who said he had forwarded the views of the chairman and secretary of the Southampton Executive Council to the Parliamentary Secretary, added to the arguments presented by Mr. King the need for retaining the interest of those who gave their time to the work of the executive councils, and the desirability of reducing the delay that followed from appeals, though he wanted the right of appeal by an aggrieved candidate to be retained.

Government Reply

Miss EDITH PITT, Parliamentary Secretary, Ministry of Health, pointed out that vacancies filled in this way represented only a small minority of total admissions to medical lists of executive councils. Last year only 168 doctors were appointed to advertised vacancies by means of this procedure, whereas over 900 were admitted in other ways. The number of applications for each advertised vacancy in 1959 averaged 24. The keenest competition was still for vacancies, especially those with substantial lists, in the southern parts of England; no fewer than 99 doctors applied for one vacancy in Hove, but several vacancies in less populated areas had fewer than 10 applicants.

She maintained that the existing system gave full scope to the local knowledge possessed by the executive council, since in their report to the Medical Practices Committee they were able to set out fully any special local circumstances as well as advising which of the candidates they considered most suitable. As the actual appointment was made by the Medical Practices Committee it was clear to all that there had been no undue local bias or prejudice in reaching the decision. The Medical Practices Committee reviewed all the applications, including those not short-listed. With the many applications received for some vacancies short lists

might exclude a large number of well-qualified candidates. At present those candidates knew that their claims were considered by a second body. But for that there might well be more appeals.

The average time for filling a vacancy was 57 days in England and Wales and 60 days in Scotland—well within the period of three months' notice required from a retiring doctor. Of the 1,075 cases in 1959 where the approval of the Medical Practices Committee was required, in less than 2% did the Committee go against the advice of the executive council and the local medical committee. Every effort was made to avoid delay. To take away the right of appeal would require legislation, and need full justification.

QUESTIONS IN THE COMMONS

Radiological Hazards to Patients

Dr. DONALD JOHNSON asked the Minister of Health on March 14 whether he was aware that the committee of inquiry on radiological hazards to patients, appointed in January, 1957, had not yet reported finally at the end of three years; and when he anticipated that the report would be received in final form.

Mr. D. WALKER-SMITH replied that the Committee on Radiological Hazards to Patients had been carrying out a very comprehensive programme of scientific investigation, and had already published an interim report on the effects of mass miniature radiography. It expected to publish a second report before the autumn. This would deal with the possible danger to future generations arising from medical radiology. Further scientific work would be needed before the hazard to the individual could be assessed, and he could not yet forecast when the committee would be able to report on this aspect.

Infected Egg-white

Mr. A. PEARSON (Pontypridd, Lab.) asked the Minister whether he was aware that routine sampling and analysis of local stocks of frozen Dutch egg-white at Pontypridd had disclosed that several of the samples were infected with food-poisoning organisms of the type which caused the recent serious outbreak of food-poisoning among schoolchildren at Pontyclun; and whether he would make it compulsory for the importation of frozen egg-white to be heat-treated prior to import into this country. Miss EDITH PITT replied that the Ministry recently gathered together a group of persons with special knowledge to examine ways of overcoming the technical difficulties of producing acceptable pasteurized egg products, including egg-whites, on a commercial basis. Until these had been overcome it would be premature to consider making heat treatment compulsory.

Assurance on Brain-washing

The PRIME MINISTER gave an unqualified assurance on March 17 that the techniques of brain-washing "have never been used by any organization responsible to the Government." He gave this answer to questions by Mr. J. CRONIN, F.R.C.S. (Loughborough, Lab.), who asked what use had been made of them by any Government department during the past 20 years for the purpose of obtaining confessions from prisoners or influencing their future conduct; and Mrs. BARBARA CASTLE (Blackburn, Lab.), who mentioned specifically the security organizations. Mr. CRONIN said the Prime Minister's answer would give widespread satisfaction; but it was unfortunate that an earlier statement had not been made, completely dissociating the country from "these abominable practices" when the matter first received publicity. Mr. H. MACMILLAN pointed out that the Secretary of State for War had made things clear as far as he was concerned, and went on: "I am grateful for the question, so that I can make it clear on behalf of the Government of this country, of whatever party, and of the whole people, that we have not, never did, and never would indulge in practices of this kind."

Mr. S. SILVERMAN (Nelson and Colne, Lab.) said there were some people in this country who would receive the statement with some surprise, having regard to their own experiences during the war. Was it not desirable to set up some commission or committee of inquiry to see whether the Prime Minister's statement was in accordance with the facts? Mr. MACMILLAN: I could not undertake to set up a committee of inquiry to find out whether what I have just said is true.

N.H.S. Psychiatrists and Interrogation

Mrs. CASTLE asked the Minister of Health on March 21 to what extent Health Service psychiatrists were made available to the Services, the police, or the security authorities for purposes of interrogation or brain-washing. Mr. D. WALKER-SMITH: No such arrangements have ever been made.

Mrs. CASTLE, commenting that Professor Alexander Kennedy did Health Service work, suggested that, in view of the conflict between Professor Kennedy's remarks and the assurance given by the Prime Minister, the Minister of Health should call on Professor Kennedy to make a public statement declaring unequivocally what he had said and what he intended to say. Mr. WALKER-SMITH replied that it was quite clear what Professor Kennedy did not say. He did not say that these techniques had ever been used in this country. The material contained in his discourse had previously been published in journals available here, and the Minister mentioned an article in the *Archives of Neurology and Psychiatry* in August, 1956.

"Preludin" Ban on April 1

Mr. SYDNEY IRVING (Dartford, Lab.) asked the Home Secretary on March 15 when the ban on the sale of "preludin" (phenmetrazine) and the 20 other substances listed by the Poisons Board except by medical prescriptions would become effective. Mr. BUTLER stated that, after considering representations, he had decided to ask the Poisons Board to reconsider the scope of their recommendation with respect to guaiphenesin. His information was that this substance was not at present available in this country in any preparation that was liable to abuse. He had also decided that no further control was necessary in respect of nialamide, which was already subject, under the Therapeutic Substances Act, 1956, to substantially the same degree of control as that recommended by the Poisons Board. With these exceptions, he hoped to put into effect, from the beginning of next month, the recommendation of the Poisons Board relating to the substances mentioned in his answer to Mr. Irving on February 11.*

Law on Suicide

The HOME SECRETARY told Mr. K. ROBINSON (St. Pancras North, Lab.) on March 17 that he could not say when the report of the Criminal Law Revision Committee on changes in the law of suicide would be received. The Committee was aware that he was anxious to have the report this summer. Mr. ROBINSON pressed him to say that, subject to the matter being satisfactorily resolved by the Committee, the Government would introduce amending legislation in the fairly near future. Mr. BUTLER said he would like to do so. It would be difficult to do it in this session, but they ought to do it in the near future, provided the report was satisfactory.

*The substances mentioned, besides preludin, guaiphenesin, and nialamide, were: acetylcarbromal; certain androgenic and oestrogenic substances administered internally; salts of azacyclonol; salts of benactyzine; salts of 3-benzylhydrazinocarbonyl-5-methyl-*iso*oxale; bromvaletone; salts of captodiame; carbromal; 2-*p*-chlorophenyl-3-methylbutane-2:3-diol; 4-hydroxymethyl-2:2-di-*iso*propyl-1:3-dioxolan; salts of hydroxyzine; salts of imipramine; esters of mephenesin; meprobamate; salts of metformin; methocarbromal; salts of α-methyl-phenethylhydrazine; salts of methyl phenidate; salts of phenelzine; salts of phenformin; salts of pipradrol; salts of rauwolfia alkaloids; salts of thalidomide; and salts of zoxazolamine.

Pay of Doctors in Armed Forces

Sir LEONARD ROPNER (Barkstone Ash, Con.) asked the Minister of Defence whether he would give an assurance that any increase in the earnings of National Health Service practitioners would be accompanied by a corresponding increase in the pay of Naval, Army, and Air Force doctors.

Mr. H. WATKINSON.—No. In reviewing the pay of Service doctors there are other factors that have to be taken into account, such as the increases which they get in common with other officers of the Services.

Permission for Operations on Children

Dr. DONALD JOHNSON (Carlisle, Con.) asked the Minister of Health on March 21 under what authority the Sheffield Regional Hospital Board was approaching magistrates with a view to establishing special juvenile courts in hospitals to intervene if parents refused permission for an operation on a child; and what plans he had for establishing similar courts in hospitals in other regions.

Mr. WALKER-SMITH stated that the Sheffield Regional Hospital Board was seeking to ensure only that the existing provisions of the Children and Young Persons Act, 1933, should, if invoked in an emergency, operate speedily. They did not need any specific authority for this, and any similar action elsewhere would be a matter for the hospital authorities concerned.

Medico-Legal

PARENTAL CONSENT TO TREATMENT*

BY

PHILIP H. ADDISON
Secretary, Medical Defence Union

A cause of action to which a hospital authority or surgeon (or both) may be liable as the result of the performance of an operation is trespass to the person in either assault or battery. Treatment administered without the patient's express or implied consent constitutes an assault which may lead to an action for damages under the civil law or a prosecution under the criminal law.

There is no rigid rule of English law that renders a minor incapable of giving his consent to the performance of an operation. Although there can be little doubt that, except in an emergency, the consent of the parent should be obtained before any operation is performed on a minor under the age of 16, opinion differs as to whether this is in fact necessary when the minor has attained that age and is capable of appreciating what it is proposed to do. The life or health of a minor of whatever age must not, of course, be jeopardized by waiting for formal parental consent: if, in an emergency, it was impracticable to obtain a relative's consent the surgeon would have a good defence provided the operation was urgent and could not reasonably be postponed.

Question of Principle

As there is no direct authority on whether the consent of a minor aged between 16 and 21 is sufficient, the question must be treated as one of principle. The rule of common law is that the consent must be freely given—i.e., without force, fear, or fraud—and by a person who is able to form a reasonable opinion upon the matter to which consent is given. For some purposes of civil law the line is drawn so that a person under 21 is under a disability, whatever his age; in so far as criminal responsibility is concerned, a person of 8 and upwards may be, and a person of 14 is, responsible for his crimes. As to the mental capacity to consent, it is surely relevant that the legislature has established a definite rule on age in cases of unlawful carnal knowledge by enacting that consent given by a child of either sex under 16 years of age shall not constitute a defence. It would seem that a distinction must be drawn between minors who have, and who have not, attained the age of 16. A distinction between the consents of these two age-groups is supported by Section 5(2) of the Mental Health Act, 1959, which provides that for informal admission the wishes of a patient of 16 shall override those of his parent or guardian. It is only reasonable to infer from this that minors of 16 and upwards are expected to assent for themselves to informal admission for treatment. The Act, by implication, validates the consent of a minor of 16 to treatment of his mental illness and dispenses with his parent's consent. It appears fair to assume that the reference to the age of 16 in Section 5(2) of the Mental Health Act, 1959, is but a restatement of the general position in law.

The National Health Service (General Medical and Pharmaceutical Services) Regulations, 1954, give all persons not under 16 years of age, and not physically and mentally incapable of doing so, the right to choose their own general medical practitioner and, by implication, to assent to procedures by him. Similarly, under the National Health Service (General Dental Services) Regulations, 1954, anyone not under 16 years of age makes his own application for dental treatment and signs the form of completion. The right now given to persons of 16 years of age and upwards to choose their own practitioner suggests that that is the effective age of choice in so far as their medical and dental treatment is concerned. As a corollary, a surgeon would be unwise to assume that the consent of the parent or guardian of a minor of 16 is equivalent to the minor's consent; the latter's consent should be obtained in every case where an adult's consent would be necessary.

Conclusion

To suggest that any surgical interference agreed to by a person of 20, for example, amounts to an assault if his parent's or guardian's consent is not also obtained is surely quite untenable. It should surely be safe to follow the legislature on the age of valid consent in sexual conduct and mental illness, and the inferences which may be drawn from the National Health Service Regulations. I submit, therefore, that, when dealing with a minor aged between 16 and 21 and able to appreciate the nature and consequences of any particular form of treatment, his own consent is all that is necessary. I appreciate that this view may conflict with long-established practice.

*Based on a contribution to the medico-legal symposium at the Joint B.M.A./C.M.A. Meeting in Edinburgh, held on July 21, 1959.

DOCTOR'S DRUG ADDICTION CRUELTY

[FROM OUR LEGAL CORRESPONDENT]

On February 11 a wife was granted a decree nisi of divorce against her doctor husband, on the ground of cruelty (*The Times*, February 11). The cruelty relied on by the wife was her husband's addiction to drugs.

The court accepted the wife's evidence that as a result of taking barbiturate drugs her husband's speech and stance were at times unsteady in 1952, and by 1955 he was losing control of his hands and frequently collapsed. Despite several expressions of repentance, he failed to break his habit, which affected his wife's health severely, causing her to lose weight and develop asthma. The husband did not defend the action, but it was adjourned to this date for the assistance of legal argument from the Queen's Proctor. The court required argument on the question whether the facts amounted to cruelty in law, for the court was satisfied that the husband had no desire to injure his wife but was merely a slave to his addiction.

Cruelty in Divorce Law

In the law of divorce, a plea of cruelty is not sufficiently made out simply by proving cruel conduct and resulting injury to health: it must also be shown that the cruel conduct was in some way "aimed at" the petitioner. Where the conduct consists of words or actions actually directed at the petitioner there is no need to prove a desire to injure. But, before the present decision, where the conduct did not consist of direct action against the petitioner most lawyers thought that a desire to injure must be proved to make out a plea of cruelty. The category of indirect action includes misconduct such as drunkenness, or crime, or addiction to drugs: and the view was that, if drunkenness, for instance, were indulged in solely for selfish gratification and not out of vindictiveness towards the other spouse, there was no cruelty in law. The new decision makes it clear that in cases of indirect misconduct there is now no need to prove a desire to injure so long as the misconduct was intentionally indulged in by the spouse and was such that it in fact caused injury to the other spouse. This decision is an application of the general common law rule that, in the absence of evidence to the contrary, the doer of an act must be taken to foresee the natural consequences of his act; and, if with that foresight he does that act, he intends all those consequences, though he may not desire them.

In the present case there was no possibility of evidence to the effect that the husband did not foresee the natural consequences of his acts. As a doctor he must have known what effect his acts would have on his wife's health. He had to be taken in law as having intended to injure her, though he had no desire to do so. His conduct therefore amounted to cruelty.

Universities and Colleges

UNIVERSITY OF OXFORD

Dr. A. G. M. Weddell has been reappointed Reader in Human Anatomy from October 1, 1960, to September 30, 1967.

Dr. the Hon. Margaret A. Jennings has been reappointed University Demonstrator in Pathology, and Dr. Edith Bülbring, F.R.S., University Demonstrator in Pharmacology, both from October 1, 1960, to September 30, 1965.

Dr. A. G. Sanders has been reappointed Senior Research Officer in Pathology from October 1, 1960, to September 30, 1965.

In Congregation on February 27 the following degrees were conferred:

D.M.—R. A. Bruce.
B.M.—R. J. Lunt, D. I. Fry.

The Board of the Faculty of Medicine has co-opted Dr. A. H. T. Robb-Smith for the statutory period of two years from the first day of Trinity Term, 1960.

UNIVERSITY OF CAMBRIDGE

The following candidates have been approved at the examination indicated:

M.CHIR.—I. S. M. Jones, R. C. Shepherd, E. F. Soothill, W. G. Williams.

In Congregation on February 20 the degree of M.B. was conferred on A. J. Costello and E. H. Richards.

Dr. J. A. Hislop has been reappointed an Assistant Director of Research in the Department of Human Ecology from October 1, 1960, for five years.

In Congregation on March 5 the following degrees were conferred:

M.D.—A. G. Ackerley, J. C. Barker.
M.CHIR.—*I. S. M. Jones.
M.B.—*N. A. Atalla, *P. J. F. Baskett, *S. Harcourt-Webster.
*By proxy.

UNIVERSITY OF ST. ANDREWS

Dr. J. Gordon Sprunt has been appointed to a Lectureship in Therapeutics in the Department of Pharmacology and Therapeutics, Queen's College, Dundee, with effect from April 1, 1960.

UNIVERSITY OF ABERDEEN

The honorary degree of LL.D. will be conferred on Lady Baird, M.B., Ch.B., Chairman of the North-eastern Regional Hospital Board, Scotland, and Sir David Campbell, Regius Professor of Materia Medica in the University from 1930 to 1959, and President of the General Medical Council, on July 8; and on Dr. Robert S. Aitken, Vice-chancellor of the University of Birmingham and Chairman of the Committee of Vice-Chancellors and Principals, on September 15.

Dr. Campbell Murray has been appointed second Medical Officer, Student Health Service, from May 1, 1960, and Dr. M. B. Roberts temporary Lecturer in Materia Medica (Experimental Pharmacology) from July 1, 1960, to September 30, 1961.

UNIVERSITY OF LONDON

The following have been recognized as teachers of the University in the subjects in parentheses: *London School of Hygiene and Tropical Medicine*, Dr. Stanley Bell (Tropical Medicine). *Institute of Diseases of the Chest*, Dr. J. R. Bignall and Dr. Joseph Smart (Medicine). *London Hospital Medical College*, Dr. M. A. Floyer and Dr. J. T. Wright (Medicine).

The degree of M.S. was awarded to E. Parry-Jones on January 8.

The degree of M.D. was awarded to P. A. Gardiner, L. Michaels, and P. A. Zorab on January 27.

The following candidates have been approved at the examinations indicated:

ACADEMIC POSTGRADUATE CERTIFICATE IN TROPICAL MEDICINE AND HYGIENE.—D. Botero, B. E. Nunez.

ACADEMIC POSTGRADUATE CERTIFICATE IN APPLIED PARASITOLOGY AND ENTOMOLOGY.—D. R. Dietlein, B. J. Elce, Susan E. Endicott, T. Jalayer, G. S. Nelson, K. K. Ødegaard, Judith N. Pleaden, N. N. Raditapole, J. N. Raybould, C. Teesdale, Margaret Tu.

Dr. J. H. Green, Senior Lecturer in Physiology at Middlesex Hospital Medical School, has been appointed to the University Readership in Physiology tenable at that School.

UNIVERSITY OF BIRMINGHAM

The following appointments are announced: Dr. R. F. Reynolds, temporary Lecturer in Anatomy; Mr. R. J. Mills, William E. Dunn Research Associate in the Department of Medicine; Mr. B. Atkins, Research Associate in the Department of Paediatrics and Child Health.

The title of Reader in Social Medicine has been conferred on Dr. C. R. Lowe, Senior Lecturer in Social Medicine; that of Honorary Reader in Medicine on Dr. J. M. French, Honorary Senior Lecturer in Medicine, and a member of the external scientific staff of the Medical Research Council; and that of Honorary Lecturer in the Department of Experimental Pathology on Dr. J. P. Bull, Director of the Medical Research Council's Industrial Injuries and Burns Research Unit, Birmingham Accident Hospital.

UNIVERSITY OF LEEDS

Mr. C. P. Mills has been appointed Clinical Lecturer in Otology from October 1, 1959, and Dr. V. Wright, Lecturer in the Department of Medicine (for rheumatism research) from January 1, 1960.

UNIVERSITY OF SHEFFIELD

The following appointments are announced: Dr. Margaret M. Platts, full-time Lecturer in Medicine; Dr. H. A. Salmon, full-time Assistant Lecturer in Physiology; Drs. J. D. Howard and O. H. Simms, part-time Instructors in Anaesthetics.

Dr. R. M. H. McMinn has resigned from the post of Lecturer in Anatomy on his appointment to a Readership in Anatomy in King's College in the University of London, and Dr. G. M. J. Fenton has resigned from the appointment of Demonstrator in Anatomy.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

FACULTY OF ANAESTHETISTS

The annual election to the Board of the Faculty took place on March 9 when the following were declared elected to the Board after a postal ballot:

Representing the Fellows: Dr. M. D. Nosworthy (re-elected), Dr. J. A. Lee, Dr. G. Jackson Rees, Dr. W. D. Wylie.

Representing the Members: Dr. R. V. Sturton.

At a meeting of the Council of the College held on March 10, with Sir James Paterson Ross, Bt., President, in the chair, the Honorary Medal of the College was presented to Sir Cecil Wakeley, Bt., Past President, in recognition of his distinguished labours for the College.

Miss Isabella Forshall, Mr. P. G. G. Martin, Mr. G. E. Moloney, and Professor A. W. Kay, who had previously been elected *ad eundem* to the Fellowship, were formally admitted.

The Hallett Prize was presented to John Coundley Doyle, of the University of Melbourne, and Handcock Prizes to S. J. McDonald (Charing Cross) and D. R. Harvey (Guy's).

The twenty-ninth Macloghlin Scholarship was awarded to A. S. Coulson, of Hendon Grammar School.

A Diploma of Fellowship in the Faculty of Anaesthetists was granted to I. M. Hallack.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS

At a meeting of the Faculty held on January 4, with the President, Mr. Arthur Jacobs, in the chair, the following were admitted Fellows of Faculty: *qua Physician*, M. A. Jafri; *qua Surgeon*, M. M. I. Fakhr, C. N. Hudson, D. G. Jones.

SCOTTISH CONJOINT BOARD

The following candidates, having passed the final examinations, have been granted the diploma of L.R.C.P.Ed., L.R.C.S.Ed., L.R.F.P.&S.Glas.:

D. T. M. Calderwood, M. R. Campbell, K. C. Clarke, G. I. Cohen, D. Crookenden, Liane C. Florin, N. G. Hamilton, Stella Pak-Ngor Ho, A. S. Jackson, Botio Kalcev, Sybil F. Kinghorn, Aspi N. Kotwall, E. T. Nagy, W. H. Williams.

ROYAL AUSTRALASIAN COLLEGE OF SURGEONS

The following, having satisfied the Court of Examiners, were admitted to Fellowship of the College by the Council on February 19:

J. D. Aberdeen, R. C. Bennett, J. B. Binks, V. G. Bulteau, R. L. Cantamessa, J. L. Castle, T. J. Claffey, F. J. Collins, T. I. Cope, W. J. Cumming, B. J. Dooley, R. G. Elmslie, J. B. Fethers, B. W. Fox, J. H. Greer, F. J. Gray, K. L. Hayes, A. H. T. Hodgkinson, R. S. B. Hudson, D. S. Leitch, W. P. Lennon, C. D. Levis, R. C. W. Lowe, W. G. Lucas, M. G. Maguire, W. B. Maguire, V. C. Marshall, K. J. Millar, R. M. Mitchell, P. F. Mountford, J. J. Murugasu, D. H. McClymont, N. L. Newman, B. McC. O'Brien, J. H. Pryor, Julien Reich, R. G. Rushworth, B. P. Scrivener, C. A. Shearer, L. T. Stretton, J. G. Sweeney, N. V. Sweeney, C. G. Thevathasan, T. J. Thwaite, P. C. Tuckfield, J. McB. White, D. C. Wilson, A. S. Wood.

FACULTY OF ANAESTHETISTS

The following, having satisfied the Court of Examiners, were admitted to Fellowship of the Faculty of Anaesthetists, Royal Australasian College of Surgeons, by the Council on February 19:

V. G. Balmer, A. G. Bradford, S. R. Gairns, J. E. D. Lane, J. E. O'Donnell, C. H. Pryor.

Vital Statistics

Scottish Vital Statistics for 1959

At the end of 1959 the population of Scotland was estimated to be 5,202,800. According to a preliminary statement issued by the Registrar-General the death rate in Scotland (12.1 per 1,000 in 1959) has varied little for a number of years. While the infant mortality, at 28.4 per 1,000 live births, was a little higher than that (27.7) in 1958, the maternal mortality, at 0.4 per 1,000 live births, was the lowest ever recorded in Scotland. Deaths from tuberculosis amounted to 577, about half the figure recorded five years ago. There was only one death from acute poliomyelitis compared with 16 in 1958. Deaths from coronary thrombosis increased from 9,923 in 1958 to 10,086 in 1959: deaths among males (6,409) greatly exceeded those among females (3,677). Deaths from cancer of the respiratory system—2,042 males and 409 females—were a little in excess of the figures recorded in 1958. Deaths from road traffic accidents (634) were only two more than in the previous year.

The expectation of life at birth (65.9 years for males and 71.4 years for females calculated on 1959 statistics) is now 21 more years for boys and 24 more years for girls than for children born at the beginning of the century. The proportion of married persons in the population is now about 60%, compared with 50% fifty years ago.

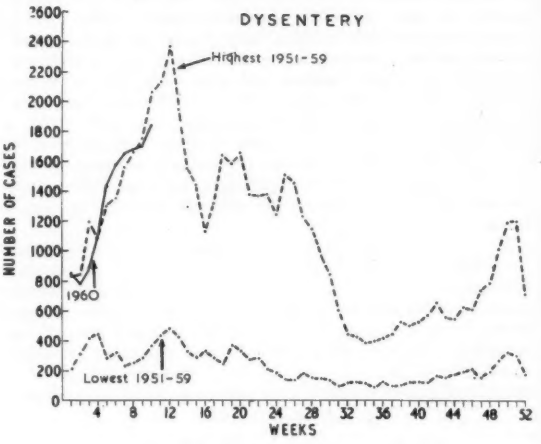
The total "net migration" of 21,500 from Scotland was made up by 6,400 who went overseas and 15,100 who went to other parts of the United Kingdom, mainly England.

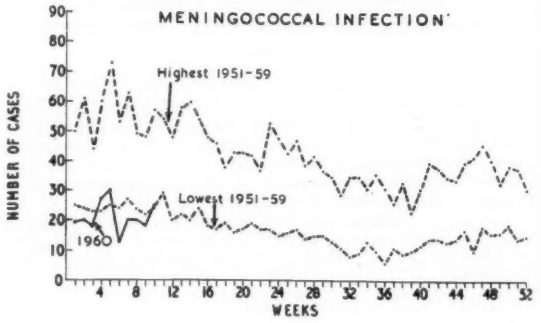
Influenza in England and Wales

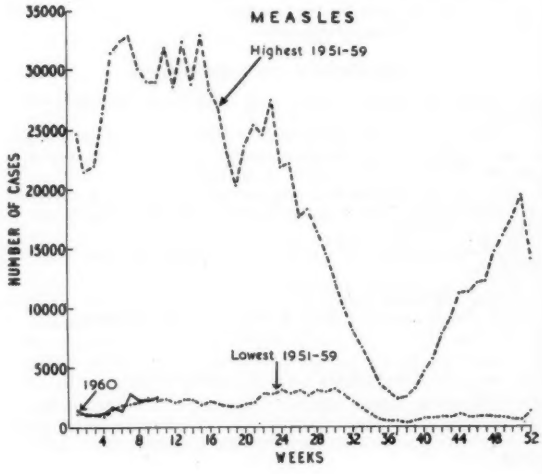
The deaths from influenza (35), bronchitis (675), and pneumonia (708), and the notifications of pneumonia (501), were all lower in the week ended March 12 than in the previous week. Although these and other indices of winter respiratory illness have continued to fall, some evidence of recent infection by influenza virus has been found in a few sporadic cases.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Mar. 5	Mar. 12
Paratyphoid Fever		
Lancashire	1	**10**
Liverpool C.B.	0	**5**
Manchester C.B.	0	**5**
Diphtheria		
Devonshire	0	**2**
Plymouth C.B.	0	**2**
Dysentery		
Cheshire	36	**64**
Wallasey C.B.	5	**13**
Hazel Grove and Bramshall U.D.	0	**13**
Macclesfield R.D.	6	**22**
Essex	111	**89**
Maldon M.B.	11	**12**
Romford M.B.	45	**38**
Gloucestershire	37	**80**
Bristol C.B.	27	**45**
Hampshire	9	**31**
Winchester R.D.	0	**10**
Kent	30	**40**
Deal M.B.	20	**15**
Lancashire	451	**454**
Bolton C.B.	25	**35**
Liverpool C.B.	52	**60**
Oldham C.B.	63	**55**
Preston C.B.	30	**50**
Ashton-under-Lyne M.B.	44	**27**
Audenshaw U.D.	2	**10**
Swinton and Pendlebury U.D.	29	**54**
Walton-le-Dale U.D.	10	**15**
Worsley U.D.	33	**10**
Preston R.D.	27	**10**
London	203	**196**
Fulham	12	**16**
Islington	26	**24**
Southwark	43	**38**
Middlesex	58	**85**
Edmonton M.B.	21	**44**
Norfolk	125	**97**
Norwich C.B.	63	**47**
East Dereham U.D.	10	**23**
Nottinghamshire	39	**43**
Nottingham C.B.	14	**15**
Carlton U.D.	8	**19**
Suffolk	13	**23**
Ipswich	12	**23**
Wiltshire	46	**38**
Swindon M.B.	19	**24**
Yorkshire North Riding	16	**36**
Redcar M.B.	11	**11**
Flaxton R.D.	0	**15**
Yorkshire West Riding	114	**155**
Bradford C.B.	24	**62**
Leeds C.B.	21	**21**
Sheffield C.B.	39	**33**
Glamorganshire	52	**67**
Bridgend U.D.	0	**18**
Ogmore and Garw U.D.	32	**32**
Rhondda M.B.	6	**10**
Glasgow	121	**108**
Edinburgh	31	**21**

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **March 5** (No. 9) and corresponding week 1959.

Figures of *cases* are for the counties shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria	2	0	0	0	3	3	1	1	0	1
Dysentery	1,706	203	264	12	8	973	82	146	11	2
Encephalitis, acute	2	0	0	0		1	0		0	
Enteric fever:										
Typhoid	1	0	0	0	1	1	0	0	0	
Paratyphoid	2	0	0	0		6	1	0	0	
Food-poisoning	268	50	12	1		112	18	3	1	
Infective enteritis or diarrhoea under 2 years				13	27				10	22
Measles*	2,355	95	70	18	24	23,512	1360	897	677	888
Meningococcal infection	18	0	8	0		37	3	19	1	3
Ophthalmia neonatorum	25	2	5	0		21	4	3	0	
Pneumonia†	596	38	202	12	7	2,583	162	674	23	38
Poliomyelitis, acute:										
Paralytic	6	1	0	0	2	9	2	1	0	
Non-paralytic	3	1	0			0	0	0		
Puerperal fever§	210	36	9	2		284	35	10	0	
Scarlet fever	1,142	35	90	48	25	1,207	50	65	37	11
Tuberculosis:										
Respiratory	447	59	60	16		444	56	66	4	
Non-respiratory	61	6	8	3		61	2	17	3	
Whooping-cough	798	72	182	8	60	500	28	42	59	85

DEATHS	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria	0	0	0	0	1	0	0	0	0	1
Dysentery	0	0		0		1	1		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years		0	0	3	0	8	0	2	0	1
Influenza	42	1	0	1	1	1,399	103	28	5	7
Measles		0	0	0	0		1	0	0	0
Meningococcal infection		0	3				0	0		
Pneumonia	859	63	42	13	12	1,809	146	82	26	19
Poliomyelitis, acute	2	0		0	0	2	1		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	93	2	10	1	5	147	12	9	0	2
Non-respiratory		3	0	0	1		0	0	0	0
Whooping-cough	0	0	0	0	1	0	0	0	2	1
Deaths 0–1 year	364	42	31	8	19	369	32	34	12	11
Deaths (excluding stillbirths)	12,163	955	705	157	204	15,551	1407	860	164	238
LIVE BIRTHS	16,074	1287	1100	278	453	15,642	1424	1082	276	378
STILLBIRTHS	282	23	22			327	24	25		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Chair of Surgery, St. Bartholomew's Hospital Medical College

Mr. G. W. TAYLOR, reader in surgery at St. Bartholomew's Hospital Medical College, has been appointed from October 1 to the London University chair of surgery, tenable there. He succeeds Sir JAMES PATERSON ROSS, P.R.C.S., who is retiring.

Mr. Taylor, who is 39 years of age, qualified from St. Bartholomew's Hospital, London, in 1943. After serving with the R.A.M.C. he held a house-surgeon appointment at Edgware General Hospital and took the F.R.C.S. in 1948. In 1949 he was appointed research assistant to the surgical professorial unit at St. Bartholomew's Hospital, and in 1950 as a Fulbright scholar was awarded a surgical fellowship at Stanford University, San Francisco. In 1951 he was appointed chief assistant in the surgical professorial unit at St. Bartholomew's Hospital, and in 1952 was awarded the B.M.A. Walter Dixon Research Scholarship. In 1955 he took the M.S. degree and was appointed reader in surgery and surgeon to St. Bartholomew's Hospital. His published work includes papers on peripheral vascular disease, lymphoedema, and wound infection.

Chair of Pharmacology, Leeds University

Dr. D. R. WOOD has been appointed to the chair of pharmacology at Leeds University from September 1. He succeeds Professor W. A. BAIN, D.Sc.

Dr. Wood went on from Brasenose College, Oxford, to complete his medical studies at the Radcliffe Infirmary. He won the Radcliffe Prize in clinical medicine in 1943 after having graduated B.A. in 1942 and B.Sc. in 1943. In 1945 he graduated B.M., B.Ch., and M.A. a year later. In 1947 Dr. Wood was awarded the George Herbert Hunt Travelling Scholarship of the University of Oxford, and in 1955 he became James Hudson Brown Postdoctoral Fellow and Squibb Fellow, Yale University Medical School. From 1942 to 1945 Dr. Wood was part-time demonstrator in the department of pharmacology at Oxford and from August, 1945, to January, 1946, he held the post of resident house-physician to Dr. F. G. Hobson at the Radcliffe Infirmary, Oxford From 1946 to 1952 he lectured in pharmacology in the department of pharmacology and therapeutics at the University of Sheffield, and from 1952 to 1957 was senior lecturer in that department. For one year, 1955 to 1956, he was senior research fellow in the department of pharmacology at Yale Medical School, and from 1957 to the present time he has been associate professor of pharmacology at McGill University, Montreal, Canada.

Medical Society of London

Dr. RONALD COVE-SMITH, who presided last week at the 180th anniversary dinner of the Medical Society of London, was deservedly complimentary about the speech of the guest of honour, Sir ARTHUR BRYANT. Proposing the toast to the society, Sir Arthur remarked that he had not been able to find much about medicine in history, and then proceeded to quote some exceedingly appropriate advice given to physicians in the fourteenth century and to describe some of the more dubious methods of treatment then in vogue. He ended by suggesting that the medical profession might consider speaking "to those who rule us and remind them that the purpose of all social and political action is to enable man to live according to his own nature." The toast of the guests was proposed by Mr. GUY BLACKBURN, and in his reply Dr. GEORGE F. ABERCROMBIE said that if there were doubts about how to distribute the money allocated by the Royal Commission for the payment of distinction awards to general practitioners, then it was worth bearing in mind that the College of General Practitioners was appealing for funds for building and other purposes.

Conferences and the Press

The Association of British Science Writers has prepared a 31-page booklet (edited by Mr. Ronald Bedford) called *A Guide to Press Arrangements for Scientific, Medical and Technical Conferences.* It is published by the British Association for the Advancement of Science, 18, Adam Street, Adelphi, London, W.C.2 (price 2s. plain, 3s. interleaved.)

"Much of the research work done in Britain to-day," the booklet says, "is paid for, directly or indirectly, by the taxpayer. He needs to know, in the clearest terms, how his money is being spent, what are the benefits he can reasonably expect to obtain, and the significance and possible consequences of new discoveries," and it discusses, very clearly and simply, the way in which properly organized press arrangements can help to achieve this end. There are useful chapters on what facilities journalists need and expect; on the various sections of the press—news agencies, the dailies, the evening papers, radio, and T.V., technical journals, and so on; on organization for the press; on press summaries; and a points-to-remember chapter which includes an admirable word of warning against the "gimmick" approach to news conferences.

Rise in Strontium-90

The amount of strontium-90 in bone in Great Britain was higher in samples examined during the first six months of 1959 than in the previous year. The increase was noted in the age groups up to 20 years, but not over that age. The samples of bone are obtained at necropsy and include material from stillbirths. The mean number of strontium units found in bones from children who had died before the age of 5 years was 2.8; the highest was 6.9 (a 14-months-old child in Lancashire).—*Radioactive and Natural Strontium in Human Bone: U.K. Results for 1959*, Part 1, 1960 (H.M.S.O., 1s. 9d.).

John Locke's Library

Eleven manuscript volumes of JOHN LOCKE'S papers and some 835 of his printed books, including presentation copies from Sir HANS SLOANE, have been given to the Bodleian Library, Oxford, by Mr. PAUL MELLON, an American collector and a Cambridge graduate. (*The Times Literary Supplement*, March 11.)

John Locke, the philosopher, studied medicine at Oxford in the early 1660's in order to keep his studentship at Christ Church without taking holy orders. His practice appears to have been confined mainly to the family of ASHLEY, later EARL OF SHAFTESBURY, though a few of his notes on other patients are preserved in the British Museum. In 1668 Locke operated on Ashley for an internal abscess and kept it drained with a silver tube—a fact gleefully exploited by contemporary satirists. He was a friend of the physician, THOMAS SYDENHAM, who declared that no man of his time was superior to Locke in judgment and manners. (Portrait by courtesy of Radio Times Hulton Picture Library.)

College of General Practitioners' Library

The honorary librarian of the College of General Practitioners would be grateful to receive any of the following types of documents:

(1) Reprints—two copies, if possible—of any published work on a medical subject by general practitioners, whether old or recent. (2) Any document or object throwing light on the history of general practice in the United Kingdom or elsewhere, including old case records, interesting letters, account books, biographical papers or books, portraits or instruments. (3) Certain books on the history of medicine in general.

Prospective donors are asked to communicate first with the Honorary Librarian, The College of General Practitioners, 41, Cadogan Gardens, London, S.W.3.

Trinity College Library Appeal

Trinity College, Dublin, is appealing for donations, large or small, to its Library Extension Appeal. At least another £300,000 must be raised this year if building is to begin in 1961. Trinity graduates or other well-wishers are asked to send their donations to the Trinity College Library Extension Appeal at either Trinity College, Dublin, or 109, New Bond Street, London, W.1.

New Antipodean Libraries

A Sydney philanthropist, Mr. ADOLPH BASSER, has given the Academy of Science, Canberra, £A.25,000 to establish a library dealing with the history of science in Australia. The Basser Library is intended to be a centre for research into scientific history, as well as a storehouse for scientific and personal documents.

To mark his eighty-eighth birthday, Sir ERNEST DAVIS, a former Mayor of Auckland and a well-known New Zealand citizen, has given £35,000 towards building a medical library and lecture hall in the grounds of Auckland Hospital. His gift includes £10,000 for books for the library.

Great Ormond Street Appeal

The Medical School of the Hospital for Sick Children, Great Ormond Street—known as the Institute of Child Health—is appealing for £400,000 to build a new five-story medical school.

The school, which is outside the scope of the National Health Service, trains specialists in paediatrics from all over the world, and its work is now seriously handicapped by the lack of teaching space and the inadequacy of the school's laboratory equipment. Donations and inquiries may be addressed to the Medical School Appeal, Institute of Child Health, Hospital for Sick Children, Great Ormond Street, London, W.C.1. (CHA 2536.)

Part-time Consultants' Research Posts

The desirability of establishing posts in which part of the time is devoted to a consultant appointment in a hospital and part of the time to research has recently been much discussed. In order to encourage this kind of research, and to see if, in fact, there is a demand for this rather novel kind of appointment, the Royal College of Physicians is advertising some of its research fellowships. See advertisement page 55 under heading Royal College of Physicians, Joseph White Research Trust.

Edinburgh Hospital Administration Course

In 1959 the department of public health and social medicine of Edinburgh University instituted a new course—leading to the Diploma of Medical Services Administration—to prepare medical and non-medical candidates for careers in hospital administration at various levels. The University is now inviting applications for six Nuffield Provincial Hospitals Trust grants (of £500) for the course beginning on October 11. Further details of these grants can be found on advertisement page 56.

Safety in Mines

The Ministry of Power's Safety in Mines Research Establishment has just published its 37th annual report. (*Safety in Mines Research 1958*, H.M.S.O., price 5s. net.)

Research projects include work on pneumoconiosis which follows the same broad lines as in previous years and is aimed at linking the incidence and progress of the disease with the concentration and character of dusts breathed by miners.

Nuffield Foundation Grant

The Nuffield Foundation have offered a grant of £60,000 for the erection of a hearing and speech centre attached to the Royal National Throat, Nose, and Ear Hospital and its associated Institute of Laryngology and Otology. The new centre will be concerned with the diagnosis, assessment, and development of hearing and speech in children suffering from impairment or total loss of these faculties, with research, and with the special training of doctors and other professional workers. Building will begin within the next few months.

Empire Rheumatism Council

A grant of £23,000, which will partly be used to help research workers in the Commonwealth, has been received by the Empire Rheumatism Council from the Geigy Pharmaceutical Co. Ltd. It will be spread over the next seven years to provide travelling fellowships for selected research workers.

"Biochemical Journal's" New Address

The editorial office of the *Biochemical Journal* has moved from the Lister Institute to the following address. All communications should be addressed to the Secretary to the Editorial Board, the *Biochemical Journal*, 133–5, Oxford Street, London, W.1.

Gift to the Middlesex

The Middlesex Hospital has been given £140,000 by Major and the Hon. Mrs. MACDONALD-BUCHANAN to build a new training school for student nurses.

The hospital owns the site of the new building, which will adjoin the main nurses' home and will house the preliminary training school, along with the main nursing school, and be equipped with modern classrooms, lecture rooms, and libraries. It is hoped that the school will be ready for use in two years.

News About People

Dr. M. D. MACKENZIE, formerly director of epidemiological services at the Ministry of Health, has been appointed by the Regional Office for Europe of the World Health Organization as adviser to the Government of Morocco in the organization of health services in Agadir.

Mr. S. A. S. MALKIN, a past-president of the British Orthopaedic Association, has been appointed a member of the Industrial Injuries Advisory Council.

COMING EVENTS

"Venereal Diseases."—I.T.V. (Granada) programme, March 30, 10 p.m. Factual report, produced with the co-operation of the Ministry of Health, on these diseases, their nature, incidence, effects, and treatment.

Horder Centres for Arthritics—1960 Appeal.—Royal première, "Once More With Feeling." Leicester Square Theatre, March 31, 8 p.m. H.R.H. Princess MARGARET has graciously promised to attend. Tickets (10s. 6d. to 25 guineas) from Première Office, 33, Orange Street, London, W.C.2 (TRA 6363).

Cambridge Medical Society.—Dinner, Corpus Christi College, April 6, at 7.15 p.m. Details from Dr. G. F. WRIGHT, 22, Parkside, Cambridge.

British Tuberculosis Association.—Provincial meeting. Southampton, April 8–9; including "The Treatment of Chronic Bronchitis—a Report of the B.T.A. Trial, Winter, 1958–9." Details from the B.T.A., 59, Portland Place, London, W.1 (MUS 3810).

School Medical Officers.—One-day course, Heatherwood Orthopaedic Hospital, Ascot, 10 a.m., April 23. Details from Mr. G. P. ARDEN, 1, Dorset Road, Windsor.

Chest and Heart Association Church Services.—London and Edinburgh, May 1; Llandaff, Cardiff, May 15. Orders of service from Chest and Heart Association, Tavistock House North, Tavistock Square, London, W.C.1.

Laboratory Animals Centre.—Symposium: "The Provision of Animals for Cancer Research," the Royal Society of Medicine, Wimpole Street, London, May 23. Details from the Centre, M.R.C. Laboratories, Woodmansterne Road, Carshalton, Surrey.

9th German Congress: Recent Advances in Medicine.—Berlin, June 8 to 12. Details from Dr. H. W. SCHRÖDER, Kongressgesellschaft für ärztliche Fortbildung e.V., 21, Klingsorstrasse, Berlin-Steglitz, Germany.

International Symposium on Drugs Affecting Lipid Metabolism.—Milan, Italy, June 2–4. Sponsored by Institute of Pharmacology, Milan University. Details from Professor S. GARATTINI, c/o Institute of Pharmacology, 21, Via A. del Sarto, Milan, Italy.

Indian Medical Association (Great Britain).—Annual dinner dance, May 5, 7.30 p.m., Carlisle Suite, Cumberland Hotel, Marble Arch, London, W.1. Guests of honour: Sir JAMES PATERSON ROSS, P.R.C.S., and Lady Ross. Tickets (37s. 6d. per head) from Dr. S. KARANI, 273, Upton Road, Bexley, Kent.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

JOURNAL OF NEUROLOGY, NEUROSURGERY, AND PSYCHIATRY.—Issued quarterly (£3 annually). The new issue (Vol. 23, No. 1) includes:

A Clinical and Electrical Study of Ulnar Nerve Lesions in the Hand. Peter Ebeling, R. W. Gilliatt, and P. K. Thomas.

Effects of Posterior Root Section on the Activity of Some Muscles in Man. P. W. Nathan and T. A. Sears.

Observations on 500 Cases of Migraine and Allied Vascular Headache. George Selby and James W. Lance.

Neurological, Electroencephalographic, and Heredo-familial Aspects of Pseudohypoparathyroidism and Pseudo-pseudohypoparathyroidism. L. G. Dickson, Y. Morita, E. J. Cowsert, J. Graves, and J. S. Meyer.

Hartnup Disease in Psychiatric Practice: Clinical and Biochemical Features of Three Cases. L. A. Hersov and R. Rodnight.

Congenital, Static Familial Ophthalmoplegia. F. Lees.

A Clinical Trial of Dehydroepiandrosterone (Diandrone). A. D. Forrest, J. Drewery, K. Fotherby, and S. G. Laverty.

A Rating Scale for Depression. Max Hamilton.

Clinical and Electromyographic Studies of "Spinal Reflexes" in Premature and Full-term Infants. I. Fényes, Ch. Gergely, and Sz. Tóth.

Fatal Encephalopathy in Glandular Fever. J. D. Bergin.

The Incidence and Characteristics of Lewy Bodies in Idiopathic Paralysis Agitans (Parkinson's Disease). J. Bethlem and W. A. den Hartog Jager.

Proceedings of the Society of British Neurological Surgeons: 60th Meeting.

Book Reviews.

OPHTHALMIC LITERATURE FOR 1958.—Issued quarterly (£4 4s. annually). The new issue (Vol. 12, No. 6: 3,726–5,231) contains abstracts from current literature.

OPHTHALMIC LITERATURE FOR 1959.—Issued quarterly (£4 4s. annually). The new issue (Vol. 13, No. 3: 1,313–2,178) contains abstracts from current literature.

ABSTRACTS OF WORLD MEDICINE.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

APPOINTMENTS

ADAMS, D. P., M.B., Ch.B., D.P.H., Deputy Medical Officer of Health and Deputy Principal School Medical Officer for Huddersfield.

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—J. M. S. Hague, M.B., B.S., F.R.C.S.Ed., Surgical Registrar (Casualty), Ipswich and East Suffolk Hospital, Anglesea Road Wing; T. J. Kitson Merritt, M.B., B.S., D.P.M., Assistant Psychiatrist, Department of Child and Family Psychiatrist, Ipswich and East Suffolk Hospital; A. T. Cartmell, M.B., Ch.B., Surgical Registrar, Stamford and Rutland Hospital; R. G. Gold, M.B., B.S., M.R.A.C.P., Medical Registrar, Regional Cardiac Unit, Papworth Hospital; A. J. Baxi, M.B., B.S., Registrar in Thoracic Surgery, Regional Thoracic Surgery Unit, Papworth Hospital; Ruth E. Young, M.B., B.S., Registrar in Psychiatry, Fulbourn and Addenbrooke's Hospitals; H. P. Jayanandaiah, M.B., B.S., D.T.M.&H., Medical Registrar, Foxhall Hospital, Ipswich; Miss R. Anklesari, M.B., B.S., Anaesthetic Registrar, United Norwich Hospitals.

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—F. M. Elderkin, M.B., B.S., M.R.C.P.Ed., D.C.H., and M. Kinsbourne, M.B., B.Ch., M.R.C.P., Medical Registrars; Y. E. Hsia, B.M., B.Ch., M.R.C.P., and D. M. Danks, M.D., M.R.A.C.P., House-physicians; R. P. Callaghan, M.B., B.S., House-surgeon; J. P. Stanfield, M.D., M.R.C.P., D.C.H. Senior Medical Registrar; I. W. Blackstone, M.B., B.Ch., House-Surgeon.

LIVERPOOL REGIONAL HOSPITAL BOARD.—J. V. Occleshaw, M.B., Ch.B., D.M.R.D., Whole-time Consultant Radiologist to Regional Neurosurgical Centre.

MACFARLANE, DAVID A., M.Ch., F.R.C.S., Consultant Surgeon to Princess Beatrice and St. Stephen's Hospitals, Chelsea.

NORTH-WEST METROPOLITAN REGIONAL HOSPITAL BOARD.—N. B. McDiarmid, M.B., B.S., D.P.M., Assistant Psychiatrist (S.H.M.O.), Hill End Hospital; P. H. Simmons, M.B., B.S., F.F.A. R.C.S., Consultant Anaesthetist, Royal Northern Hospital; Helen M. Mayer, M.R.C.S., L.R.C.P., M.R.C.O.G., Consultant Gynaecologist, Harrow Hospital; L. R. Twentyman, M.B., B.Chir., F.F.Hom., Consultant Homoeopathic Physician, Royal London Homoeopathic Hospital; H. J. Shaw, B.M., B.Ch., F.R.C.S., Consultant Ear, Nose, and Throat Surgeon, Northwood, Pinner, and District Hospital; E. L. Trickey, M.B., B.S., F.R.C.S., Consultant Orthopaedic Surgeon, Edgware General Hospital, and Royal National Orthopaedic Hospital Country Branch, Stanmore (Joint Appointment); S. R. Reynolds, M.B., B.Chir., D.M.R.E., Consultant Radiologist, West Herts and St. Paul's Hospitals, Hemel Hempstead.

ZOOB, MAX, M.D., M.R.C.P., Consultant Cardiologist (part-time), Preston Hall Hospital.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, March 28

MANCHESTER MEDICAL SOCIETY: SECTION OF GENERAL PRACTICE.—At Large Anatomy Theatre, Manchester University Medical School, 8.30 for 9 p.m., Dr. R. S. F. Schilling: Chronic Respiratory Disease in Cotton Workers.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Edridge-Green Lecture by Dr. R. A. Weale: Duplicity Theory of Vision.

Tuesday, March 29

BONE AND TOOTH SOCIETY.—At Nuffield Department of Orthopaedic Surgery, Oxford, 2 p.m., symposium: The Matrix.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1959-1960.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Professor Ludo van Bogaert (Antwerp): Disseminated Sclerosis, To-day's Great Imitator.

ROYAL STATISTICAL SOCIETY: MEDICAL SECTION.—At Manson Theatre, London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. Cedric A. B. Smith: Some Statistical Problems in Human Genetics.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. T. Rowland Hill: Neurology.

Wednesday, March 30

MANCHESTER MEDICAL SOCIETY.—At Large Anatomy Theatre, Manchester University Medical School, 4 for 4.30 p.m., meeting of Fellows. Professor W. W. Mushin: Some Problems of Controlled Respiration.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor J. D. Griffiths: Dissemination of Cancer Cells During Operative Procedures.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Miss Barbara M. Naish: Home Accidents—A Social Responsibility (illustrated).

Thursday, March 31

FACULTY OF HOMOEOPATHY.—5 p.m., Dr. Douglas Ross: Peptic Ulcer.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., annual meeting. Dr. Charles S. McKendrick: Phonocardiography.

MANCHESTER MEDICAL SOCIETY: SECTION OF ANAESTHETICS.—At Staff House, Manchester University, 7.45 for 8 p.m., Dr. F. T. Evans: Mistakes I Have Made.

ROYAL COLLEGE OF SURGEONS OF ENGLAND AND INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Otolaryngology Lecture by Mr. D. W. C. Northfield: Brain Tumours.

Friday, April 1

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., Mr. William McKenzie: Aural Vertigo—Management.

WHIPPS CROSS HOSPITAL MEDICAL SOCIETY.—8.30 p.m., Dr. James Graham: Trends in Medicine from the Administrators' Point of View.

Sunday, April 3

UNIVERSITY COLLEGE HOSPITAL.—10.15 a.m., meet in Front Hall of main Hospital. Lecture-demonstration for general practitioners. Dr. T. A. J. Prankerd: The Anaemias.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Clarke-Williams.—On March 15, 1960, to Shirley, wife of Dr. Michael Clarke-Williams, of Linden House, Eye, Suffolk, a brother for Marion and Adam—Jeremy.

Grey-Turner.—On March 20, 1960, to Lilias, wife of Dr. Elston Grey-Turner, a daughter.

Robins.—On February 23, 1960, at Exeter, to Shirley and Robert Robins, a third child—James Edward.

Sartory.—On March 7, 1960, at Nuffield House, Guy's Hospital, London, S.E., to Pamela (formerly Johnson) and Francis B. Sartory, M.R.C.S., L.R.C.P., L.D.S., a sister for Geoffrey, Ghislaine, Rosemary, and Jonathan—Louise Gay.

DEATHS

Bennett.—On February 25, 1960, Maud Bennett, L.R.C.P.&S.Ed., L.R.F.P.S., aged 92.

Blaiklock.—On February 26, 1960, at 1, Crossway, Jesmond, Newcastle upon Tyne, Northumberland, John Pearson Blaiklock, M.B., B.S., aged 50.

Braithwaite.—On February 26, 1960, in hospital, Edward Wrigley Braithwaite, M.R.C.S., L.R.C.P., of 25, Ashfield Road, Shipley, Yorks, late of Park Square, Leeds, Yorks.

Briggs.—On March 3, 1960, at Eastbourne, Sussex, Norman Briggs, C.I.E., M.R.C.S., L.R.C.P., D.P.H., colonel, I.M.S. retired, aged 68.

Burrell.—On February 27, 1960, at his home, 30, Melville Street, Ryde, Isle of Wight, Arthur Ambrose Burrell, M.B., B.Ch., aged 80.

Cameron.—On February 25, 1960, at Law Hospital, Carluke, Lanarkshire, Allison Weir Cameron, M.B., Ch.B., formerly of Edinburgh.

Campbell.—On March 2, 1960, at his home, Cortworth, Piers Road, Borrowdale, Southern Rhodesia, Ian Colin Campbell, M.B., Ch.B., D.Obst.R.C.O.G.

Cartwright.—On March 2, 1960, at his home, Lansdowne, Cloister Crofts, Leamington Spa, Warwicks, John Fraser Cartwright, M.R.C.S., L.R.C.P.

De Lavis-Trafford.—On February 26, 1960, at Beaulieu-sur-Mer, France, Marcus Antonius Johnston de Lavis-Trafford, C.V.O., O.B.E., M.D., aged 79.

Groves.—On February 25, 1960, John Nixon Groves, D.S.O., M.B., B.Ch., of The Priory, Ledbury, Herefordshire.

Hosegood.—On March 1, 1960, at Southmead Hospital, Bristol, Reginald Andrew Hosegood, L.R.C.P.&S.Ed., L.R.F.P.S.

Montgomery.—On February 27, 1960, at his home, Dial Cottage, Highcliffe, Hants, Samuel Alexander Delmege Montgomery, M.B., B.Ch., late of Bournemouth, Hants.

Morris.—On February 28, 1960, James Kincaid Williamson Morris, M.B., Ch.B., of Avenue Road, Doncaster, Yorks, aged 78.

Norman.—On March 1, 1960, John Charles Norman, M.B., B.S., of 5, Chatsworth Gardens, Eastbourne, Sussex, late of Hebburn upon Tyne, Co. Durham.

Tasker.—On March 2, 1960, at Kuala Lumpur, Malaya, Peter William Gedge Tasker, M.D., aged 35.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Cold Agglutinins in Virus Pneumonia

Q.—*What is the value of demonstrating the presence of cold agglutinins in influenza and virus pneumonia, and what is the recommended technique? At what time in the course of the illness do they appear?*

A.—The value of demonstrating cold haemagglutinins in influenza is of little importance, as their presence has not been shown to be associated with infection by the three known influenza viruses, A, B, and C. However, in the case of virus pneumonia the presence of cold agglutinins may be of diagnostic significance. Pneumonia may be caused by infection with many rickettsiae and viruses—e.g., *R. burneti* (Q fever), psittacosis, influenza, adenoviruses, measles, etc.—none of which is associated with the development of cold agglutinins. The latter have only been found associated with some infections by Eaton's virus, and even here recent work has suggested that there may be no direct relationship. In recent years cold-agglutinin-positive pneumonias have formed only a relatively small proportion of laboratory-tested suspected virus pneumonias, and few outbreaks have been reported since 1945, though an outbreak in a boys' school in East Anglia was described in 1956.[1]

Cold agglutinins are non-specific, and to be of diagnostic significance in respiratory disease a fourfold rise in titre between acute and convalescent sera is desirable. The serum in influenza will not show a significant cold agglutinin titre, whereas in approximately 50%[2] of patients with virus pneumonia cold agglutinins have been found; however, a negative result cannot exclude virus pneumonia.

The patient's serum is separated at 37° C., after which it may be stored at 0–4° C. for short periods or at −20° C. for at least three years without appreciable loss of titre. "Doubling" dilutions of the serum are made in tubes, and to each is added an equal volume of 1% suspension of normal human Group O corpuscles. The tubes are left at 20° C. (room temperature) for 2 hours, after which the agglutination titre is read. The suspensions are then remixed and kept in the refrigerator at 4° C. for at least 2 hours. The agglutination titre should be read immediately the tubes are removed from the refrigerator, and then all tubes are placed at 37° C. for 1 hour to demonstrate the disappearance of agglutination on warming.[3] All sera from a patient should be tested on the same day and positive and negative controls included in the test.

An alternative method of testing for cold haemagglutinins may be found in *Diagnostic Procedures for Virus and Rickettsial Diseases*.[4]

Cold haemagglutinins may be detected in virus pneumonia during the second week of the illness, whereas maximum titres usually occur during the third or fourth week.

REFERENCES

1 Wood, P., *Brit. med. J.*, 1956, **1**, 711.
2 Horsfall, F. L., jun., *Ann. intern. Med.*, 1947, **27**, 275.
3 Dacie, J. V., *Practical Haematology*, 1956, 2nd ed., p. 121. Churchill, London.
4 American Public Health Association Committee, *Diagnostic Procedures for Virus and Rickettsial Diseases*, 1956, 2nd ed., p. 272. New York.

Treatment for Gummatous Ulcer

Q.—*What is the treatment for a gummatous ulcer in a 70-year-old man with a positive W.R.?*

A.—It is important to distinguish between a gummatous ulcer and a non-syphilitic ulcer in a patient who has positive serological tests for syphilis. If, for instance, a patient was adequately treated for late syphilis long ago his serological tests may well remain positive even though he is no longer syphilitic. Lesions which develop in later years, including ulcers of the leg or elsewhere, are apt to be attributed to syphilis although due to some other cause. The diagnosis must be based on clinical findings, the result of biopsy, and perhaps by response to treatment.

If the patient concerned has a gummatous ulcer it is likely to respond to intramuscular injections of bismuth (e.g., 0.3 g. of bismuth metal or one of its insoluble salts, such as the salicylate or oxychloride, intramuscularly weekly for 3 to 4 weeks) and potassium iodide by mouth in a mixture containing 5 or 10 grains to the dose, three times a day. This can be followed by injections of penicillin (e.g., procaine penicillin in oily suspension containing 2% of aluminium monostearate, 600,000 units intramuscularly daily for 10 days). Healing should be prompt and satisfactory. Occasionally, in the case of a patient with gummatous ulcer of the lower leg who also has venous stasis, it happens that healing may be delayed or prevented. In such a case treatment for the circulatory condition is also required.

If the patient has active syphilis, the importance of full investigation, including tests of the cerebrospinal fluid, and examination of other members of the family, should not be overlooked.

Lobeline and Smoking

Q.—*I have read that buffered lobeline ("bantron") has been used in America as a means of stopping smoking, and I should be glad of your views on its efficacy and its availability.*

A.—Many smokers who wish to break themselves of the habit fail because when they attempt to do so they experience disturbing withdrawal symptoms. These are, at least in part, due to the sudden removal of the addicting drug, nicotine. The pharmacological actions of lobeline resemble those of nicotine, and it has been suggested that this substance could be used as a "crutch" by the smoker during the period in which withdrawal symptoms might occur. Early experience showed that, although lobeline had some effect in reducing the desire to smoke, its side-effects, which were mainly gastro-intestinal, were most unpleasant. Rapp and Olen[1] found that if lobeline was combined with gastric antacids not only were the gastro-intestinal effects much reduced but also that the amount of lobeline required to exert a deterrent effect was reduced. In a well-controlled clinical trial, using a double-blind technique, they showed that the substance "bantron," which contains 2 mg. lobeline sulphate and at least 100 mg. of a mixture of slow- and fast-acting antacids, definitely reduced the desire of heavy smokers to smoke. Within a period of six days 80% of those who received the active preparation had stopped smoking. This, however, was an acute experiment and they mention that at the end of one month only 53% of those who had received the lobeline preparation for a week were still not smoking. If the drug had been continued it is possible that a better result than this might have been obtained, but it is also possible that the smokers might have become addicted to bantron instead of tobacco. Bantron is a proprietary preparation marketed by the Campana Corporation, Batavia, Illinois, U.S.A., and does not appear to be available in this country. The composition of the preparation is such that it would not be difficult for any chemist to make up a similar mixture.

REFERENCE

1 Rapp, G. W., and Olen, A. A., *Amer. J. med. Sci.*, 1955, **230**, 9.

Wind Instruments and Asthma

Q.—*Is the playing of wind instruments, such as the oboe, to be encouraged in children with asthma?*

A.—There is no doubt that the playing of wind instruments is more difficult for a child with asthma than for a normal child, and there are likely to be times when an asthmatic could not play a wind instrument at all. It is unlikely that the breath control necessary for playing an oboe would be beneficial, even though breathing exercises have been shown to be of value in asthmatics, and it might possibly increase the tendency to overdistension of the lungs.

Asthma, though it tends to improve in childhood and during young adult life, has a tendency to return later. It would therefore not be desirable for a child taking up music to be encouraged to play wind instruments.

Allergy to Contraceptives

Q.—*A patient is violently allergic to rubber sheaths. He is allergic to other substances on contact, and would probably develop sensitivity to chemical spermatocides. If his wife were to wear a dutch cap type of appliance and he were to use cortisone ointment prophylactically to prevent rubber contact allergy would he be free from risk, or might he become sensitive to the cortisone?*

A.—Multiple epidermal allergies to unrelated substances are not at all common, and it therefore does not seem very likely that this patient would be sensitive to chemical spermatocides. If a patch test with a spermatocide on the normal skin gave negative results it might be best for him to try a chemical contraceptive. This might turn out to be a better solution than the third one suggested. Allergy to hydrocortisone is very uncommon but is known to occur, and so is allergy to the ointment base in which it may be incorporated. However, it is not certain that the application of hydrocortisone would protect against rubber dermatitis when exposure was often repeated. Cortisone ointment used prophylactically might be effective, but it is not free from risk.

Removal of Mammary Hair

Q.—*A woman in her mid-twenties has a growth of hair around the mammary areolae. How could it be removed and prevented from recurring?*

A.—Hair in this situation is usually entirely suitable for epilation by electrolysis or diathermy. For this it is necessary that individual hairs should be well developed so that the follicle is easily seen and entered by the needle.

Blood Counts and Phenylbutazone Therapy

Q.—*Are occasional blood counts necessary in patients on prolonged phenylbutazone treatment, and, if so, how often?*

A.—Occasional blood counts are desirable but not an absolute necessity in patients on prolonged phenylbutazone therapy. In some cases sore throat, fever, or malaise may precede any changes in the circulating blood by several days. Should these symptoms occur, singly or together, an estimation of the white cells should be done. It is advisable, but not essential, to have a white-cell estimation done before and after the first 10–20 days' therapy, but in most clinics and practices counts are done subsequently only if symptoms arise.

Unpleasant Smell and Taste

Q.—*A patient lost his taste and smell about a year ago after bronchitis which was treated with tetracycline hydrochloride. They have returned to some extent, but everything has a tarry flavour and smell which is most obnoxious. Can anything be done about this?*

A.—The most likely explanation of this odd story appears to be that during antibiotic treatment superinfection with a resistant organism occurred, with involvement of the olfactory mucosa, the persistence of which is responsible for the present symptoms. The presence of an unpleasant smell is always rather suggestive of a sinus infection, which should be excluded. An actual loss of taste and smell is suggestive of an "allergic" type of rhinitis, and perhaps the bronchitis was of the asthmatoid type. Both a clinical and a bacteriological examination of the nose and nasopharynx, including radiography of the sinuses and full allergic investigation, are necessary before it can be decided whether anything might be done. It is to be hoped that a catarrh lasting for a year has not led to atrophic or other changes which are irreversible. The presumed infection might well respond to treatment, possibly local in the form of a spray or snuff, with a sulphonamide or antibiotic to which the causative organism is sensitive.

Nasal Crusting

Q.—*Is there any treatment for chronic "crusting" in the nose?*

A.—When the crusting arises deep in the nasal passages, then the condition is one of atrophic rhinitis. This, fortunately, is much less common in England than formerly, and requires regular cleansing treatment every day to keep the passages free from crusts. On the other hand, there is quite a common form of nasal crusting around the mucocutaneous junction in the nasal vestibule. This can be troublesome and painful, but it nearly always responds to regular application of ung. hyd. ox. flav. dil. to each nasal vestibule on a piece of wool night and morning.

Tuberculosis from Telephones

Q.—*What is the risk of infection with tuberculosis from telephones? Can it be diminished?*

A.—Tubercle bacilli are carried in droplets which are projected only when the infected person coughs. It is unlikely that any person would cough directly into the mouthpiece when using a telephone, and therefore the danger of cross-infection from the instrument is probably very small. Nevertheless, the mouthpiece should be thoroughly wiped each day with a swab moistened with an antiseptic solution such as sol. chloroxylenol. B.P. This procedure should be carried out by a responsible person who will be careful to see that no actual liquid gets into the telephone mechanism.

NOTES AND COMMENTS

Sterilizing Needles.—Dr. W. M. PENNY (London, S.E.20) writes: Surely the simplest way to sterilize a Hagedorn needle is to hold it momentarily in a flame. Personally I have a Bunsen burner on my mantelpiece; or one can use a match and wipe off the soot with cotton soaked in an antiseptic. Louis Pasteur, as you will remember, passed his hands through a flame. But how effective this was, of course, I do not know.

OUR EXPERT replies: Hepatitis virus(es) in blood are apparently more resistant than other viruses to the usual inactivating agents—e.g., infective serum after being heated for 4 hours at 60° C. still produced hepatitis in volunteers. It is probable that, if one has cleaned a Hagedorn needle under running water and wiped it thoroughly with cotton-wool, heating the needle until red hot in a Bunsen burner would be effective, but just a quick pass through it might not be. There have been outbreaks of serum hepatitis in patients in clinics and sanatoria where the collection of blood by finger puncture with a needle "sterilized" by flame from a spirit lamp was the only procedure to which transmission could be attributed. Although Dr. Penny has used the flame of a match, one could not recommend it as a reliable procedure. Unfortunately the absolute answer to this problem must await the isolation of the virus(es).

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